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L69 64 DUP REM L68 (16 DUPLICATES REMOVED)

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L69 ANSWER 1 OF 64 USPATFULL on STN
ACCESSION NUMBER: 2004:63352 USPATFULL
TITLE: Methods employing and compositions containing plaque associated molecules for prevention and treatment of atherosclerosis
INVENTOR(S): Harats, Dror, Ramat Gan, ISRAEL
George, Jacob, Petah Tikva, ISRAEL

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 2004047870	A1	20040311	
APPLICATION INFO.:	US 2003-451370	A1	20030702	(10)
	WO 2002-IL5		20020103	

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: Sol Sheinbein, G E Enrlich, C/O Antonhy Castorina Suite 207, 2001 Jefferson Davis Highway, Arlington, VA, 22202
NUMBER OF CLAIMS: 16
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 2 Drawing Page(s)
LINE COUNT: 1588
AB Methods and compositions employing plaque associated molecules effective in inducing mucosal tolerance and inhibiting inflammatory processes contributing to atheromatous **vascular disease** and sequalae are provided.

L69 ANSWER 2 OF 64 USPATFULL on STN
ACCESSION NUMBER: 2004:50764 USPATFULL
TITLE: System for exsanguinous metabolic support of an organ or tissue
INVENTOR(S): Brasile, Lauren, Albany, NY, UNITED STATES
PATENT ASSIGNEE(S): Breonics, Inc., Otisville, NY (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 2004038193	A1	20040226	
APPLICATION INFO.:	US 2003-650986	A1	20030827	(10)
RELATED APPLN. INFO.:	Division of Ser. No. US 2000-547843, filed on 12 Apr 2000, GRANTED, Pat. No. US 6642045			

	NUMBER	DATE
PRIORITY INFORMATION:	US 1999-129257P	19990414 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: HESLIN ROTHENBERG FARLEY & MESITI PC, 5 COLUMBIA CIRCLE, ALBANY, NY, 12203
NUMBER OF CLAIMS: 36
EXEMPLARY CLAIM: 1

NUMBER OF DRAWINGS: 2 Drawing Page(s)
LINE COUNT: 1939
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB An exsanguinous metabolic support system for maintaining an organ or tissue at a near normal metabolic rate is disclosed. The system employs a warm perfusion solution capable of supporting the metabolism of the organ or tissue thereby preserving its functional integrity. The system also monitors parameters of the circulating perfusion solution, such as pH, temperature, osmolarity, flow rate, **vascular** pressure and partial pressure of respiratory gases, and regulates them to insure that the organ is maintained under near-physiologic **conditions**. Use of the system for long-term maintenance of organs for transplantation, for resuscitation and repair of organs having sustained warm ischemic damage, as a pharmaceutical delivery system and prognosticator of posttransplantation organ function is also disclosed.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L69 ANSWER 3 OF 64 USPATFULL on STN
ACCESSION NUMBER: 2004:50763 USPATFULL
TITLE: System for exsanguinous metabolic support of an organ or tissue
INVENTOR(S): Brasile, Lauren, Albany, NY, UNITED STATES
PATENT ASSIGNEE(S): Breonics, Inc., Otisville, NY (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2004038192	A1	20040226
APPLICATION INFO.:	US 2003-443452	A1	20030522 (10)

RELATED APPLN. INFO.: Continuation-in-part of Ser. No. US 2001-849618, filed on 4 May 2001, GRANTED, Pat. No. US 6582953
Continuation-in-part of Ser. No. US 2000-547843, filed on 12 Apr 2000, GRANTED, Pat. No. US 6642045

	NUMBER	DATE
PRIORITY INFORMATION:	US 1999-129257P	19990414 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: HESLIN ROTHENBERG FARLEY & MESITI PC, 5 COLUMBIA CIRCLE, ALBANY, NY, 12203
NUMBER OF CLAIMS: 10
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 2 Drawing Page(s)
LINE COUNT: 2256
AB An exsanguinous metabolic support system for maintaining an organ or tissue at a near normal metabolic rate is disclosed that employs a warm perfusion solution capable of altering the production of nitric oxide (NO) in an organ or tissue and supporting the metabolism of the organ or tissue at normothermic temperatures. Perfusion with the solution of the invention, therefore, can be used to regulate nitric oxide production in situations where it is desirable to do so, for example, to prevent reperfusion injury. The system also monitors parameters of the circulating perfusion solution, such as pH, temperature, osmolarity, flow rate, **vascular** pressure and partial pressure of respiratory gases, and nitric oxide (NO) concentration and regulates them to insure that the organ is maintained under near-physiologic **conditions**. Use of the system for long-term maintenance of organs for transplantation, for resuscitation and repair of organs having sustained warm ischemic damage, to treat cardiovascular **disorders**, to prevent reperfusion injury, as a pharmaceutical delivery system and prognosticator of posttransplantation organ function is also disclosed.

L69 ANSWER 4 OF 64 USPATFULL on STN

ACCESSION NUMBER: 2004:32292 USPATFULL
TITLE: Device, systems and methods for localized heating of a vessel and/or in combination with MR/NMR imaging of the vessel and surrounding tissue
INVENTOR(S): Yang, Xiaoming, Baltimore, MD, UNITED STATES
Atalar, Ergin, Columbia, MD, UNITED STATES
Yeung, Christopher, Pikesville, MD, UNITED STATES
PATENT ASSIGNEE(S): The Johns Hopkins University School of Medicine (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2004024434	A1	20040205
APPLICATION INFO.:	US 2003-404903	A1	20030401 (10)

	NUMBER	DATE
PRIORITY INFORMATION:	US 2002-369241P	20020401 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: EDWARDS & ANGELL. LLP, P.O. Box 9169, Boston, MA, 02209
NUMBER OF CLAIMS: 49
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 7 Drawing Page(s)
LINE COUNT: 1948
AB Featured are devices, systems and methods for localized heating of a vessel as well as devices, systems and methods for MR/NMR imaging of a vessel while locally heating a portion of the vessel. More particularly featured are such devices, systems and methods for use when administering or delivering therapeutic agents including genes and/or drugs to the tissues of the vessel. Such a method includes positioning a thermal energy delivery device proximal a target site of an internal the vessel of a body and activating the thermal energy delivery device so as to heat the target site thereby locally increasing a temperature of tissue at the target site. In further embodiments, the method includes introducing a therapeutic medium to the target site over a predetermined time period, and wherein said activating occurs at least one of before, during or after said step of introducing.

L69 ANSWER 5 OF 64 USPATFULL on STN
ACCESSION NUMBER: 2004:30732 USPATFULL
TITLE: Methods and compositions for modulating the immune system and uses thereof
INVENTOR(S): Chen, Lan Bo, Lexington, MA, UNITED STATES
Kraeft, Stine-Kathrein, Dorchester, MA, UNITED STATES
Auclair, Daniel, Ashland, MA, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2004022869	A1	20040205
APPLICATION INFO.:	US 2002-307916	A1	20021202 (10)

	NUMBER	DATE
PRIORITY INFORMATION:	US 2001-334121P	20011130 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: PENNIE AND EDMONDS, 1155 AVENUE OF THE AMERICAS, NEW YORK, NY, 100362711
NUMBER OF CLAIMS: 49
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 1 Drawing Page(s)
LINE COUNT: 5354
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention provides methods of preventing, treating or

ameliorating one or more symptoms of disorders in which modulation of a subject's immune system is beneficial utilizing a lymphoid tissue inducing agent and an immunomodulatory agent. In particular, the present invention provides methods of preventing, treating or ameliorating a proliferative disorder, an infectious disease, a cardiovascular disease, an autoimmune disorder, or an inflammatory disorder or one or more symptoms thereof comprising administering to a subject in need thereof one or more lymphoid tissue inducing agents and one or immunomodulatory agents. The present invention also provides compositions and articles of manufacture for use in preventing, treating or ameliorating one or more symptoms associated with disorders in which modulation of a subject's immune system is beneficial, including, but not limited to proliferative disorders, infectious diseases, cardiovascular diseases, autoimmune disorders and inflammatory disorders. The present invention further provides methods for screening and identifying lymphoid tissue inducing agents and/or immunomodulatory agents.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L69 ANSWER 6 OF 64 BIOTECHDS COPYRIGHT 2004 THOMSON DERWENT/ISI on STN
ACCESSION NUMBER: 2003-20338 BIOTECHDS
TITLE: Generating an enhanced immune response in a subject comprises administering to the subject an immunogenic stimulus (e.g. a tumor-associated antigen) and an agonistic 4-1BB-binding agent (e.g. antibody that binds to 4-1BB); tumor-associated antigen, antibody and dendrite cell for use in disease therapy and gene therapy
AUTHOR: CHEN L; STROME S E
PATENT ASSIGNEE: MAYO FOUND MEDICAL EDUCATION and RES
PATENT INFO: WO 2003049755 19 Jun 2003
APPLICATION INFO: WO 2002-US32364 9 Oct 2002
PRIORITY INFO: US 2001-328004 9 Oct 2001; US 2001-328004 9 Oct 2001
DOCUMENT TYPE: Patent
LANGUAGE: English
OTHER SOURCE: WPI: 2003-532879 [50]
AN 2003-20338 BIOTECHDS
AB DERWENT ABSTRACT:

NOVELTY - Generating an enhanced immune response in a subject comprising **administering** to the subject an immunogenic stimulus and an agonistic 4-1BB-binding agent, is new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following: (1) an in vitro method of activating a T-cell, comprising providing a cell sample having a T-cell, and culturing the sample with an immunogenic stimulus and an agonistic 4-1BB-binding agent; and (2) preventing induction of anergy or of reversing anergy in a T-cell, comprising contacting the T-cell with the immunogenic stimulus and agonistic 4-1BB-binding agent.

BIOTECHNOLOGY - Preferred Method: In generating an enhanced immune response in a subject, the agonistic 4-1BB-binding agent is an antibody that binds to 4-1BB, or a 4-1BB ligand (4-1BBL) or its functional fragment. The immunogenic stimulus is a polypeptide, a tumor-associated antigen (TAA), or a functional fragment of TAA. The TAA is a molecule produced by a cancer cell selected from leukemia, lymphoma, neurological cancer, melanoma, breast cancer, lung cancer, head and neck cancer, gastrointestinal cancer, liver cancer, pancreatic cancer, genitourinary cancer, prostate cancer, renal cell cancer, bone cancer and **vascular** cancer. The immunogenic stimulus may also be a molecule produced by an infectious microorganism such as a virus (e.g. retrovirus), a bacterium, a fungus or a protozoan parasite. The subject is a human. Additionally, the immunogenic stimulus is a dendritic cell comprising a major histocompatibility complex (MHC) molecule with a bound peptide-epitope, where the peptide-epitope is a fragment of a TAA or a fragment of a polypeptide produced by an infectious microorganism. The MHC molecule is MHC class I or II molecule. The immune response is a response of a T-cell. The T-cell is a CD8+ or CD4+ T-cell. In addition, the immunogenic stimulus is a hybrid cell. The hybrid cell is a fusion

product of a tumor cell and a dendritic cell. The immunogenic stimulus may also be a tumor cell, a dendritic cell that has been incubated with tumor cell, a tumor lysate or a **heat-shock protein** bound to peptide-epitope of protein expressed by a tumor cell. The tumor cell is transfected with or transformed with a nucleic acid encoding a cytokine or a growth factor. The cytokine is granulocyte macrophage-colony stimulating factor (GM-CSF). In preventing induction of anergy or of reversing anergy in a T-cell, the contacting is in vitro. The T-cell is in a mammal, particularly a human. The contacting comprises **administering** to the mammal the immunogenic stimulus and the agonistic 4-1BB-binding agent, a nucleic acid encoding the immunogenic stimulus and the agonistic 4-1BB-binding agent, the immunogenic stimulus and a nucleic acid encoding the agonistic 4-1BB-binding agent, or a nucleic acid encoding the immunogenic stimulus and a nucleic acid encoding the agonistic 4-1BB-binding agent. The nucleic acid encoding the immunogenic stimulus and the nucleic acid encoding the agonistic 4-1BB-binding agent are in the same nucleic acid molecule. The method comprises **administering** a cell transfected or transduced with a nucleic acid encoding the immunogenic stimulus or the agonistic 4-1BB-binding agent to the mammal, where the cell is a cell, or a progeny of a cell, that prior to the transfection or transduction, was obtained from the mammal.

ACTIVITY - Immunostimulant. No biological data is given.

MECHANISM OF ACTION - Gene therapy.

USE - The method is useful in enhancing immune responses in human subjects, in reversing anergy in T-cells, or in preventing the induction of anergy in T-cells. The method may be used, for example, in the prophylaxis or therapy against infectious **diseases** or cancers.

ADMINISTRATION - The agents may be given at a dose of 0.01-100 mg/kg via oral, transdermal, intravenous, subcutaneous, intramuscular, intraperitoneal, intrarectal, intravaginal, intranasal, intragastric, intratracheal or intrapulmonary means. (40 pages)

L69 ANSWER 7 OF 64 BIOTECHDS COPYRIGHT 2004 THOMSON DERWENT/ISI on STN
ACCESSION NUMBER: 2003-23351 BIOTECHDS
TITLE: Treating a **vascular disease**, particularly atherosclerosis, thrombosis, restenosis, stent restenosis or angioplasty restenosis, by administering a Toll-like receptor-4 (TLR-4) inhibitor to a mammal; virus vector and non-virus vector-mediated MD2 receptor-specific antisense oligonucleotide or hammerhead ribozyme animal administration for use in heart disease gene therapy
AUTHOR: ARDITI M; RAJAVASHISTH T; SHAH P K
PATENT ASSIGNEE: CEDARS SINAI MEDICAL CENT
PATENT INFO: US 2003077279 24 Apr 2003
APPLICATION INFO: US 2002-128166 23 Apr 2002
PRIORITY INFO: US 2002-128166 23 Apr 2002; US 2001-335637 24 Oct 2001
DOCUMENT TYPE: Patent
LANGUAGE: English
OTHER SOURCE: WPI: 2003-615988 [58]
AN 2003-23351 BIOTECHDS
AB DERWENT ABSTRACT:

NOVELTY - Treating a **vascular disease** comprises **administering** a Toll-like receptor-4 (TLR-4) inhibitor to a mammal.

DETAILED DESCRIPTION - An INDEPENDENT CLAIM is also included for a system for inhibiting the biological activity of TLR-4 comprising: (1) an intravascular device; and (2) a therapeutic composition coated upon the intravascular device, where the therapeutic composition comprises a TLR-4 inhibitor.

BIOTECHNOLOGY - Preferred Inhibitor: The TLR-4 inhibitor comprises a nucleic acid expressing antisense TLR-4 RNA, a nucleic acid encoding a soluble TLR-4 protein, a nucleic acid encoding a hammerhead ribozyme that cleaves TLR-4 mRNA, an antisense TLR-4 oligodeoxinucleotide (ODN), a nucleic acid expressing a double-stranded RNA (dsRNA) that is

sufficiently homologous to a portion of a TLR-4 gene product such that the dsRNA is capable of inhibiting the encoding function of mRNA that would otherwise cause the production of TLR-4, a protein sequence that corresponds to at least a portion of a receptor that binds to a TLR-4 ligand during a TLR-4 signal transduction event, or an anti-TLR-4 antibody. The TLR-4 protein is unable to participate in normal TLR-4 signal transduction, lacks a substantial portion of the normal TLR-4 signal transduction domain, or competes for a non-bound TLR-4 ligand (particularly a chlamydial **heat shock protein** -60 (cHSP60) or a lipopolysaccharide (LPS)). The TLR-4 inhibitor is a nucleic acid expressing the dsRNA, which further includes a sense strand (further including approximately 21 nucleotides), and an antisense strand (further including approximately 21 nucleotides). The sense strand and the antisense strand are paired such that they posses a duplex region of approximately 19 nucleotides. The sense strand and the antisense strand each further include an overhang at a 3'-terminus of approximately 2 nucleotides. The sense overhang and the antisense overhang are symmetrical. The antisense overhang comprises a UU 3'-overhang or a dTdT 3'-overhang, which is complementary to the mRNA. Preferably, at least one of the sense overhang and the antisense overhang further includes a deoxythymidine. The TLR-4 inhibitor may also be a protein sequence (10-20 amino acids) that corresponds to at least the portion of the receptor that binds to the TLR-4 ligand during the TLR-4 signal transduction event. The receptor may be a TLR-4 receptor or an MD2 receptor. The TLR-4 inhibitor is included within a vector, e.g. adenoviruses, adeno-associated viruses, retroviruses, lentiviruses, viral vectors, or non-viral vectors. Preferably, the vector is an adenovirus serotype 5-based vector. Preferred System: The intravascular device of the system comprises a catheter or a stent. The system further comprises a therapeutic composition sufficient to inhibit a **vascular disease**.

ACTIVITY - Vasotropic; Antiarteriosclerotic; Thrombolytic; Cardiant; Antiinflammatory. No biological data given.

MECHANISM OF ACTION - Toll-like Receptor-4 Inhibitor; Antisense therapy; Gene therapy.

USE - The method or the system is useful for inhibiting or treating a **vascular disease**, e.g. atherosclerosis, transplant atherosclerosis, vein-graft atherosclerosis, thrombosis, restenosis, stent restenosis, angioplasty restenosis (all claimed), or inflammation and other heart **disease**.

ADMINISTRATION - The TLR-4 inhibitor is **administered** intravenously, intramuscularly, or with an intravascular device (all claimed). (21 pages)

L69 ANSWER 8 OF 64 BIOTECHDS COPYRIGHT 2004 THOMSON DERWENT/ISI on STN
ACCESSION NUMBER: 2003-20853 BIOTECHDS
TITLE: New flow electroporation device for encapsulating allosteric effectors (e.g. inositol hexaphosphate) of hemoglobin in cells (e.g. erythrocytes) comprises walls defining a flow channel, an inlet flow portal and an outlet flow portal; flow electroporation for cell transfection with application in gene therapy of heart condition, anemia and lung disorder
AUTHOR: DZEKUNOV S M; LEE H J; LI L; SINGH V; LIU L; HOLADAY J W
PATENT ASSIGNEE: DZEKUNOV S M; LEE H J; LI L; SINGH V; LIU L; HOLADAY J W
PATENT INFO: US 2003059945 27 Mar 2003
APPLICATION INFO: US 2002-80272 21 Feb 2002
PRIORITY INFO: US 2002-80272 21 Feb 2002; US 2001-269867 21 Feb 2001
DOCUMENT TYPE: Patent
LANGUAGE: English
OTHER SOURCE: WPI: 2003-567141 [53]
AN 2003-20853 BIOTECHDS
AB DERWENT ABSTRACT:

NOVELTY - A flow electroporation device (I), is new.

DETAILED DESCRIPTION - A flow electroporation device (I) comprises: (a) walls defining a flow channel configured to receive and to

transiently contain a continuous flow of a suspension comprising particles;(b) an inlet flow portal in fluid communication with the flow channel, where the suspension can be introduced into the flow channel through the inlet flow portal; and (c) an outlet flow portal in fluid communication with the flow channel, where the suspension can be withdrawn from the flow channel through the outlet flow portal. The walls defining the flow channel comprises a first electrode plate forming a first wall of the flow channel and a second electrode plate forming a second wall of the flow channel opposite the first wall, where the area of the electrodes contact with the suspension, and the distance between the electrodes is chosen so that the thermal resistance of the flow channel is less than 4 degreesC per Watt. The paired electrodes are placed in electrical communication with a source of electrical energy, where an electrical field is formed between the electrodes. The suspension of the particles flowing through the flow channel can be subjected to an electrical field formed between the electrodes. INDEPENDENT CLAIMS are included for the following: (1) transfecting a cell, comprising providing an expression vector coding for a desired protein or peptide and introducing the vector into the cell by flow electroporation; (2) delivering a therapeutic agent to a patient, comprising incorporating the therapeutic agent into platelets by electroporation, and **administering** the platelets to the patient; and (3) treating a patient with a therapeutic protein, comprising transfecting a cell population with an expression vector that codes for the desired protein by flow electroporation.

BIOTECHNOLOGY - Preferred Device: The electrode plates in the device further comprises a gasket formed from an electrically non-conductive material and disposed between the first and second electrode plates to maintain the electrode plates in spaced-apart relation, the gasket defining a channel forming opposed side walls of the flow channel. The gasket forms a seal with each of the first and second electrode plates. The device comprises flow channels and the gasket comprises channels forming opposed sidewalls of each of the channels. One of the inlet and outlet flow portals comprises a bore formed in one of the electrode plates and in fluid communication with the flow channel. In addition, the device comprises a cooling element operatively associated with the flow channel to dissipate heat. The cooling element comprises a thermoelectric cooling element, a cooling fluid flowing in contact with the electrode, or a heat sink operatively associated with the electrode. The resistance of the flow channel is 0.5-4, preferably 1.5-2.5 degreesC per watt. The first electrode comprises an elongated, electrically conductive structure, and the second electrode comprises a tubular, electrically conductive structure. The electrodes are concentrically arranged so that the second, tubular electrode surrounds the first electrode in spaced-apart relation, and the flow channel is disposed within an annular space defined between the first and second electrodes. The electrodes form at least a portion of the walls defining the flow channel. The device may also comprise concentric annular spacers for maintaining the first and second electrodes in spaced-apart, concentric relation. The device is arranged in series or in parallel with a second, like device. Preferred Method: In transfecting a cell, 50-95, preferably 70-80 % of the cells transfected by electroporation express the desired protein or are viable. The desired protein is b-cell differentiation factor, b-cell growth factor, mitogenic cytokine, chemotactic cytokine, colony stimulating factor, angiogenesis factor, cadherin, selectin, integrin, NCAM, ICAM, L1, t-cell replacing factors, differentiation factor, transcription factor, mRNA, **heat shock protein**, nuclear protein complex, RNA/DNA oligomer, interferon (IFN)-alpha, IFN-beta, IFN-omega, interleukin (IL)1 to IL18, leptin, myostatin macrophage stimulating protein, platelet-derived growth factor, tumor necrosis factor (TNF)-alpha, TNF-beta, NGF, CD40L, CD137L/4-1BBL, human lymphotoxin-beta, TNF-related apoptosis-inducing ligand, monoclonal antibody, fragments of monoclonal antibody, granulocyte-colony stimulating factor (G-CSF), macrophage (M)-CSF, granulocyte monocyte (GM)-CSF, platelet derived growth factor (PDGF), IL1-alpha, IL-beta, fibroblast growth factor (FGF), IFN-gamma, IP-10, PF4, GRO, 9E3,

erythropoietin, endostatin, angiostatin, **vascular** endothelial growth factor (VEGF), or soluble receptor and any of their fragments or combinations. Preferably, the desired proteins are erythropoietin, endostatin, angiostatin, IL12, IL2, or their fragments. In delivering a therapeutic agent to a patient, the electroporation is flow electroporation. The therapeutic agent is AGM-1470 (TNP-470); MetAP-2; growth factor antagonists; antibodies to growth factors; growth factor receptor antagonists; TIMP; batimastat; marimastat; genistein SU5416; alphaVbeta3/5; retinoic acid; fenretinide; 1alphaepihydrocortisol, corteloxone, tetrahydrocortisone and 17alphahydroxyprogesterone; staurosporine, MDL 27032; vitamin D derivatives including 22-oxa-1 alpha, and 25-dihydroxyvitamin D3; arachidonic acid inhibitors including indomethacin and sulindac; tetracycline derivatives including minocycline; thalidomide derivatives; 2-methoxyestradiol; tumor necrosis factor-alpha; interferon-gamma-inducible protein 10 (IP-10); IL1 and IL12; IFN alpha, beta or gamma; angiostatin protein or plasminogen fragments; endostatin protein or collagen 18 fragments; proliferin-related protein; group B streptococcus toxin; CM101; CAI; troponin I; squalamine; nitric oxide synthase inhibitors including L-NAME; thrombospondin; wortmannin; amiloride; spironolactone; ursodeoxycholic acid; bufalin; suramin; tecogalan sodium; linoleic acid; captopril; irsogladine; FR-118487; triterpene acids; castanospermine; leukemia inhibitory factor; lavendustin A; platelet factor-4; herbimycin A; diaminoantraquinone; taxol; aurin-tricarboxylic acid; DS-4152; pentosan polysulphite; radicicol; fragments of human prolactin; erbstatin; eponemycin; shark cartilage; protamine; Louisianin A, C and D; PAF antagonist WEB 2086; auranofin; ascorbic ethers; or sulfated polysaccharide D 4152.

ACTIVITY - Cardiant; Vasotropic; Antiarteriosclerotic; Cerebroprotective; Antianemic. No biological data is given.

MECHANISM OF ACTION - Cell therapy.

USE - The device and methods are useful for the encapsulation of biologically active substances in various cell populations (e.g. erythrocytes) in blood by electroporation to achieve therapeutically desirable changes in the physical characteristics of the cell populations in the blood. The cells may be used for treating individuals who are experiencing lowered oxygenation of their tissues due to the inadequate function of their lungs or circulatory system, which may be due to cardiovascular or hematological **diseases**, such as heart failure, ischemia, myocardial infarction, stroke, anemia, arteriosclerosis, or blood loss. The cells may also be used to accelerate detoxification processes by improving oxygen supply, to improve the efficacy of various cancer treatments, and to enhance the athletic performance of humans or animals.

ADMINISTRATION - Treating a human or animal for any of the above **diseases** is done by transfusing 0.5-6 units of treated blood product, such as platelets. The platelets are **administered** to the patient intravenously. (All claimed.)

EXAMPLE - No relevant example given. (59 pages)

L69 ANSWER 9 OF 64 USPATFULL on STN

ACCESSION NUMBER: 2003:329826 USPATFULL

TITLE: Genes involved in immune related responses observed with asthma

INVENTOR(S): Groot, Pieter Cornelis, Den Haag, NETHERLANDS
van Bergenhenegouwen, Bram Jeroen, Utrecht, NETHERLANDS
van Oosterhout, Antonius Josephus Maria, Utrecht, NETHERLANDS

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2003232037	A1	20031218
APPLICATION INFO.:	US 2003-369214	A1	20030215 (10)

RELATED APPLN. INFO.: Continuation of Ser. No. WO 2001-NL610, filed on 16 Aug 2001, UNKNOWN

	NUMBER	DATE
PRIORITY INFORMATION:	EP 2000-202867	20000816

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: TRASK BRITT, P.O. BOX 2550, SALT LAKE CITY, UT, 84110
NUMBER OF CLAIMS: 25
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 24 Drawing Page(s)
LINE COUNT: 3285
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Asthma is one of the most common chronic diseases (155 million people worldwide) and is rapidly increasing (20-50% per decade), particularly in children (currently 10% in The Netherlands). Asthma impairs the quality of life and is a major cause of absence from school and work. Asthma, if not treated properly, can be life threatening. The invention provides a nucleic acid library comprising genes or functional fragments thereof wherein the genes are essentially capable of initiation and/or progression and/or suppression and/or repression of an immune response.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L69 ANSWER 10 OF 64 USPATFULL on STN
ACCESSION NUMBER: 2003:306440 USPATFULL
TITLE: Isolated GRP94 ligand binding domain polypeptide and nucleic acid encoding same, crystalline form of same, and screening methods employing same
INVENTOR(S): Gewirth, Daniel T., Durham, NC, UNITED STATES
Nicchitta, Christopher V., Durham, NC, UNITED STATES
PATENT ASSIGNEE(S): Duke University (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 2003215874	A1	20031120	
APPLICATION INFO.:	US 2002-260104	A1	20020930	(10)

	NUMBER	DATE
PRIORITY INFORMATION:	US 2001-326291P	20011001 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: JENKINS & WILSON, PA, 3100 TOWER BLVD, SUITE 1400, DURHAM, NC, 27707
NUMBER OF CLAIMS: 62
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 17 Drawing Page(s)
LINE COUNT: 12401
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB An isolated GRP94 ligand binding domain polypeptide, a three-dimensional crystal structure of the same, and methods of using the same to design modulators of Hsp90 proteins.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L69 ANSWER 11 OF 64 USPATFULL on STN
ACCESSION NUMBER: 2003:300801 USPATFULL
TITLE: Vaccine formulations and methods for immunizing an individual against shed antigen specific B cells
INVENTOR(S): Barbera-Guillem, Emilio, Powell, OH, UNITED STATES
Nelson, M. Bud, Worthington, OH, UNITED STATES
PATENT ASSIGNEE(S): BioCrystal, Ltd., Westerville, OH (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 2003212027	A1	20031113	
APPLICATION INFO.:	US 2003-336210	A1	20030103	(10)

RELATED APPLN. INFO.: Continuation of Ser. No. US 2000-594985, filed on 15 Jun 2000, ABANDONED

	NUMBER	DATE
PRIORITY INFORMATION:	US 1999-139521P	19990616 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: BENESCH, FRIEDLANDER, COPLAN & ARONOFF LLP, ATTN: IP DEPARTMENT DOCKET CLERK, 2300 BP TOWER, 200 PUBLIC SQUARE, CLEVELAND, OH, 44114
NUMBER OF CLAIMS: 33
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 1 Drawing Page(s)
LINE COUNT: 2035
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Provided are methods for inducing an immune response reactive with idiotypes on shed antigen-specific B cells in an individual by administering an immunologically effective amount of a vaccine formulation. Also provided are vaccine formulations comprising one or more peptides, wherein a peptide comprises an idiotype of an antibody that binds to an epitope of shed antigen; or one or more polynucleotides, wherein a polynucleotide encodes a peptide comprising an idiotype of an antibody that binds to an epitope of shed antigen.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L69 ANSWER 12 OF 64 USPATFULL on STN
ACCESSION NUMBER: 2003:294838 USPATFULL
TITLE: Medical devices and compositions for delivering anti-proliferatives to anatomical sites at risk for restenosis
INVENTOR(S): Tremble, Patrice, Santa Rosa, CA, UNITED STATES
Hendriks, Marc, Brunssum, NETHERLANDS
Carlyle, Wenda, Silverado, CA, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2003207856	A1	20031106
APPLICATION INFO.:	US 2003-392229	A1	20030318 (10)

	NUMBER	DATE
PRIORITY INFORMATION:	US 2002-365497P	20020318 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: OPPENHEIMER WOLFF & DONNELLY LLP, 840 NEWPORT CENTER DRIVE, SUITE 700, NEWPORT BEACH, CA, 92660
NUMBER OF CLAIMS: 27
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 7 Drawing Page(s)
LINE COUNT: 1240

AB Methods, compositions and devices for inhibiting restenosis are provided. Specifically, molecular chaperone inhibitor compositions and medical devices useful for the site specific delivery of molecular chaperones are disclosed. In one embodiment the medical device is a vascular stent coated with a molecular chaperone inhibitor selected from the group consisting of geldanamycin, herbimycin, macbecin and derivatives and analogues thereof. In another embodiment an injection catheter for delivery an anti-restenotic effective amount of geldanamycin to the adventitia is provided.

L69 ANSWER 13 OF 64 USPATFULL on STN
ACCESSION NUMBER: 2003:213273 USPATFULL
TITLE: Vaccine compositions and methods useful in inducing

immune protection against arthritogenic peptides involved in the pathogenesis of rheumatoid arthritis

INVENTOR(S): Carson, Dennis A., Del Mar, CA, UNITED STATES
Albani, Salvatore, Encinitas, CA, UNITED STATES

PATENT ASSIGNEE(S): THE REGENTS OF THE UNIVERSITY OF CALIFORNIA (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2003147910	A1	20030807
APPLICATION INFO.:	US 2002-299184	A1	20021118 (10)

RELATED APPLN. INFO.: Continuation of Ser. No. US 2000-616247, filed on 14 Jul 2000, PENDING Division of Ser. No. US 1998-107615, filed on 30 Jun 1998, GRANTED, Pat. No. US 6153200 Division of Ser. No. US 1996-618464, filed on 15 Mar 1996, GRANTED, Pat. No. US 5773570 Continuation-in-part of Ser. No. US 1994-246988, filed on 20 May 1994, ABANDONED

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: GARY CARY WARE & FRIENDENRICH LLP, 4365 EXECUTIVE DRIVE, SUITE 1100, SAN DIEGO, CA, 92121-2133
NUMBER OF CLAIMS: 17
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 5 Drawing Page(s)
LINE COUNT: 1066
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Vaccine compositions useful in inducing immune protection in a host against arthritogenic peptides involved in the pathogenesis of rheumatoid arthritis are disclosed. Each vaccine composition provides antigenic dnaJp1 peptide (by including the peptide or a polynucleotide which encodes the peptide) and, optionally, other peptide fragments of the microbial dnaJ protein and/or human homologs thereof. Methods for identifying persons who are predisposed to develop rheumatoid arthritis and methods for use of the inventive vaccines are also disclosed.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L69 ANSWER 14 OF 64 USPATFULL on STN
ACCESSION NUMBER: 2003:206881 USPATFULL
TITLE: Vaccine compositions and methods useful in inducing immune protection against arthritogenic peptides involved in the pathogenesis of rheumatoid arthritis

INVENTOR(S): Carson, Dennis A., Del Mar, CA, UNITED STATES
Albani, Salvatore, Encinitas, CA, UNITED STATES

PATENT ASSIGNEE(S): THE REGENTS OF THE UNIVERSITY OF CALIFORNIA (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2003143238	A1	20030731
APPLICATION INFO.:	US 2002-299540	A1	20021118 (10)

RELATED APPLN. INFO.: Continuation of Ser. No. US 2000-616247, filed on 14 Jul 2000, PENDING Division of Ser. No. US 1998-107615, filed on 30 Jun 1998, GRANTED, Pat. No. US 6153200 Division of Ser. No. US 1996-618464, filed on 15 Mar 1996, GRANTED, Pat. No. US 5773570 Continuation-in-part of Ser. No. US 1994-246988, filed on 20 May 1994, ABANDONED

	NUMBER	DATE
PRIORITY INFORMATION:	WO 1995-US4896	19950424
	WO 1997-US2957	19970220

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION

LEGAL REPRESENTATIVE: GARY CARY WARE & FRIENDENRICH LLP, 4365 EXECUTIVE DRIVE, SUITE 1100, SAN DIEGO, CA, 92121-2133
NUMBER OF CLAIMS: 17
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 5 Drawing Page(s)
LINE COUNT: 1066
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Vaccine compositions useful in inducing immune protection in a host against arthritogenic peptides involved in the pathogenesis of rheumatoid arthritis are disclosed. Each vaccine composition provides antigenic dnaJp1 peptide (by including the peptide or a polynucleotide which encodes the peptide) and, optionally, other peptide fragments of the microbial dnaJ protein and/or human homologs thereof. Methods for identifying persons who are predisposed to develop rheumatoid arthritis and methods for use of the inventive vaccines are also disclosed.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L69 ANSWER 15 OF 64 USPATFULL on STN
ACCESSION NUMBER: 2003:195096 USPATFULL
TITLE: Heat shock protein inducer
INVENTOR(S): Takahashi, Naohiko, Oita, JAPAN
Ooie, Tatsuhiko, Oita, JAPAN
Sakata, Toshiie, Oita, JAPAN
Yamanaka, Kunitoshi, Oita, JAPAN
Nawata, Tomoko, Oita, JAPAN
Arikawa, Masaya, Oita, JAPAN
Hara, Masahide, Oita, JAPAN
Saikawa, Tetsunori, Oita, JAPAN
Shimada, Tatsuo, Oita, JAPAN
Yoshimatsu, Hironobu, Oita, JAPAN

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 2003134907	A1	20030717	
APPLICATION INFO.:	US 2002-230361	A1	20020829	(10)

	NUMBER	DATE
PRIORITY INFORMATION:	JP 2002-2835	20020109

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: STERNE, KESSLER, GOLDSTEIN & FOX PLLC, 1100 NEW YORK AVENUE, N.W., WASHINGTON, DC, 20005
NUMBER OF CLAIMS: 7
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 12 Drawing Page(s)
LINE COUNT: 797
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB A heat shock protein inducer is provided for purposes of preventing or treating ischemic disease or ischemia/reperfusion injury. This heat shock protein inducer has geranylgeranylacetone as an active ingredient and induces heat shock proteins in the heart.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L69 ANSWER 16 OF 64 USPATFULL on STN
ACCESSION NUMBER: 2003:166509 USPATFULL
TITLE: Composition for the prevention and/or treatment of artherosclerosis
INVENTOR(S): Shoenfeld, Yehuda, Ramat Gan, ISRAEL
Harats, Dror, Ramat Gan, ISRAEL
George, Jacob, Petah Tikva, ISRAEL

	NUMBER	KIND	DATE

PATENT INFORMATION: US 2003114367 A1 20030619
APPLICATION INFO.: US 2001-806400 A1 20010330 (9)
WO 1999-IL519 19990930

	NUMBER	DATE
PRIORITY INFORMATION:	IL 1998-126447	19981004

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: G E Ehrlich (1995) Ltd, Anthony Castorina, Suite 207, 2001 Jefferson Davis Highway, Arlington, VA, 22202
NUMBER OF CLAIMS: 26
EXEMPLARY CLAIM: 1
LINE COUNT: 986
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB An immunological oral tolerance-inducing composition for prevention and/or treatment of atherosclerosis, comprising an active component selected from the group consisting of modified low density lipoprotein, oxidized low density lipoprotein (Ox LDL), heat shock protein 60/65 (HSP 60/65), beta2-glycoprotein-1(?2GP-1), functional derivatives thereof and mixtures thereof, in combination with a pharmaceutically acceptable carrier for oral administration.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L69 ANSWER 17 OF 64 USPATFULL on STN
ACCESSION NUMBER: 2003:140965 USPATFULL
TITLE: Arthroscopic irrigation solution and method for peripheral vasoconstriction and inhibition of pain and inflammation
INVENTOR(S): Demopulos, Gregory A., Mercer Island, WA, UNITED STATES
Palmer, Pamela Pierce, San Francisco, CA, UNITED STATES
Herz, Jeffery M., Mill Creek, WA, UNITED STATES
PATENT ASSIGNEE(S): Omeros Corporation (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2003096807	A1	20030522
APPLICATION INFO.:	US 2002-138192	A1	20020501 (10)

RELATED APPLN. INFO.: Continuation-in-part of Ser. No. US 2001-839633, filed on 20 Apr 2001, PENDING Continuation-in-part of Ser. No. WO 1999-US24672, filed on 20 Oct 1999, UNKNOWN

	NUMBER	DATE
PRIORITY INFORMATION:	US 1998-105029P	19981020 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: OMEROS MEDICAL SYSTEMS, INC., 1420 FIFTH AVENUE, SUITE 2675, SEATTLE, WA, 98101
NUMBER OF CLAIMS: 105
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 3 Drawing Page(s)
LINE COUNT: 3576
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB A method and solution for perioperatively inhibiting a variety of pain and inflammation processes during arthroscopic procedures. The solution preferably includes a vasoconstrictor that exhibits alpha-adrenergic activity and one or more additional pain and inflammation inhibitory agents at dilute concentration in a physiologic carrier, such as saline or lactated Ringer's solution. The solution is applied by continuous irrigation of a wound during a surgical procedure for peripheral vasoconstriction and inhibition of pain and/or inflammation while avoiding undesirable side effects associated with systemic application of larger doses of the agents.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L69 ANSWER 18 OF 64 USPATFULL on STN
ACCESSION NUMBER: 2003:127747 USPATFULL
TITLE: Arthroscopic irrigation solution and method for peripheral vasoconstriction and inhibition of pain and inflammation
INVENTOR(S): Demopulos, Gregory A., Mercer Island, WA, UNITED STATES
Palmer, Pamela Pierce, San Francisco, CA, UNITED STATES
Herz, Jeffery M., Mill Creek, WA, UNITED STATES
PATENT ASSIGNEE(S): Omeros Corporation (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2003087962	A1	20030508
APPLICATION INFO.:	US 2002-138193	A1	20020501 (10)

RELATED APPLN. INFO.: Continuation-in-part of Ser. No. US 2001-839633, filed on 20 Apr 2001, PENDING Continuation-in-part of Ser. No. WO 1999-US24672, filed on 20 Oct 1999, UNKNOWN

	NUMBER	DATE
PRIORITY INFORMATION:	US 1998-105029P	19981020 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: OMEROS MEDICAL SYSTEMS, INC., 1420 FIFTH AVENUE, SUITE 2675, SEATTLE, WA, 98101
NUMBER OF CLAIMS: 54
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 3 Drawing Page(s)
LINE COUNT: 3339
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB A method and solution for perioperatively inhibiting a variety of pain and inflammation processes during arthroscopic procedures. The solution preferably includes a vasoconstrictor that demonstrates substantial agonist activity at alpha adrenergic receptors and that is selected for peripheral (local) vasoconstriction and one or more additional pain and inflammation inhibitory agents at dilute concentration in a physiologic carrier, such as saline or lactated Ringer's solution. The solution is applied by continuous irrigation of a wound during a surgical procedure for peripheral vasoconstriction and inhibition of pain and/or inflammation while avoiding undesirable side effects associated with systemic application of larger doses of the agents.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L69 ANSWER 19 OF 64 USPATFULL on STN
ACCESSION NUMBER: 2003:86807 USPATFULL
TITLE: Treatment of a coronary condition by delivery of therapeutics to the pericardial space
INVENTOR(S): Hung, David T., San Francisco, CA, UNITED STATES
PATENT ASSIGNEE(S): Chiron Corporation (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2003060415	A1	20030327
APPLICATION INFO.:	US 2002-263408	A1	20021002 (10)

RELATED APPLN. INFO.: Continuation of Ser. No. US 1996-742353, filed on 1 Nov 1996, PENDING

	NUMBER	DATE
PRIORITY INFORMATION:	US 1995-7158P	19951101 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: Lisa E. Alexander, CHIRON CORPORATION, Intellectual

Property - R440, P.O. Box 8097, Emeryville, CA, 94662-8097
NUMBER OF CLAIMS: 86
EXEMPLARY CLAIM: 1
LINE COUNT: 3160
AB The invention is a treatment for coronary conditions by delivering a therapeutic agent to the pericardial space. The therapeutic agent can be delivered by internal entry through the atrium or venticle, or by external entry through the chest cavity. The therapeutic agent can be a polypeptide, polynucleotide or other drug.

L69 ANSWER 20 OF 64 USPATFULL on STN
ACCESSION NUMBER: 2003:86791 USPATFULL
TITLE: Reagents and methods for smooth muscle therapies
INVENTOR(S): Brophy, Colleen, Scottsdale, AZ, UNITED STATES
Komalavilas, Padmini, Tempe, AZ, UNITED STATES
Panitch, Alyssa, Higley, AZ, UNITED STATES
Seal, Brandon, Mesa, AZ, UNITED STATES
Lokesh, Joshi, Tempe, AZ, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2003060399	A1	20030327
APPLICATION INFO.:	US 2002-226956	A1	20020823 (10)

	NUMBER	DATE
PRIORITY INFORMATION:	US 2001-314535P	20010823 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: Kittie A. Murray LLC, c/o PortfoliolP, P.O. Box 52050, Minneapolis, MN, 55402
NUMBER OF CLAIMS: 33
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 10 Drawing Page(s)
LINE COUNT: 3114
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention provides novel polypeptides comprising heat shock protein 20 (HSP20)-derived polypeptides to treat or inhibit smooth muscle vasospasm, as well to treat and inhibit smooth muscle cell proliferation and migration.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L69 ANSWER 21 OF 64 USPATFULL on STN
ACCESSION NUMBER: 2003:79071 USPATFULL
TITLE: Characterization of GRP94-ligand interactions and purification, screening, and therapeutic methods relating thereto
INVENTOR(S): Nicchitta, Christopher V., Durham, NC, UNITED STATES
Wassenberg, James J., Durham, NC, UNITED STATES
Rosser, Meredith F.N., Durham, NC, UNITED STATES
Reed, Robyn C., Durham, NC, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2003054996	A1	20030320
APPLICATION INFO.:	US 2002-210333	A1	20020801 (10)

RELATED APPLN. INFO.: Continuation of Ser. No. WO 2001-US9512, filed on 26 Mar 2001, PENDING

	NUMBER	DATE
PRIORITY INFORMATION:	US 2000-192118P	20000324 (60)

DOCUMENT TYPE: Utility

FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: JENKINS & WILSON, PA, 3100 TOWER BLVD, SUITE 1400, DURHAM, NC, 27707
NUMBER OF CLAIMS: 133
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 17 Drawing Page(s)
LINE COUNT: 5078
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention discloses characterization of interactions between ligands and Hsp90 proteins, including GRP94, wherein ligand binding to the N-terminal nucleotide binding domain of GRP94 elicits a conformational change that converts the GRP94 from an inactive to an active conformation, and wherein the chaperone and peptide-binding activities of the GRP94 are markedly stimulated. Also disclosed are purification, screening, and therapeutic methods pertaining to the biological activity of GRP94, and in some instances HSP90, based upon the characterization of ligand interactions of Hsp90 peptide-binding proteins, including GRP94.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L69 ANSWER 22 OF 64 USPATFULL on STN
ACCESSION NUMBER: 2003:44369 USPATFULL
TITLE: Immunomodulatory peptides derived from heat shock proteins and uses thereof
INVENTOR(S): Albani, Salvatore, Encinitas, CA, UNITED STATES
Carson, Dennis A., Del Mar, CA, UNITED STATES
Prakken, Berent J., Utrecht, NETHERLANDS
Martini, Alberto, Piacenza, ITALY

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 2003031679	A1	20030213	
APPLICATION INFO.:	US 2001-1938	A1	20011031	(10)

	NUMBER	DATE
PRIORITY INFORMATION:	US 2000-245181P	20001101 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: GARY CARY WARE & FRIENDENRICH LLP, 4365 EXECUTIVE DRIVE, SUITE 1600, SAN DIEGO, CA, 92121-2189
NUMBER OF CLAIMS: 73
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 14 Drawing Page(s)
LINE COUNT: 2057
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB A method of modulating an immune response in a subject is disclosed. The invention is based on the discovery that an effective therapeutic strategy for ameliorating the inflammation-related symptoms of an immune-mediated disease, such as arthritis, can be achieved by modulation of the underlying immune response itself, rather than by merely addressing the resulting inflammation. This strategy can be used to regulate the inflammatory response and is applicable to a variety of contexts in which immune modulation is desired, such as mucosal tolerization, DNA vaccination, anergy induction, active immunization, and ex vivo modulation of antigen-specific T cells. In one embodiment, the method comprises administering to the subject a bacterial dnaJ peptide or a human homolog or a non-homologous human isoform thereof.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L69 ANSWER 23 OF 64 USPATFULL on STN
ACCESSION NUMBER: 2003:3462 USPATFULL
TITLE: Identification of gene sequences and gene products and their specific function and relationship to pathologies

in a mammal
INVENTOR(S): Jendoubi, Moncef, Bethesda, MD, UNITED STATES
PATENT ASSIGNEE(S): Milagen, Inc., Richmond, CA (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2003003497	A1	20030102
APPLICATION INFO.:	US 2002-213183	A1	20020805 (10)

RELATED APPLN. INFO.: Division of Ser. No. US 1997-906487, filed on 5 Aug 1997, ABANDONED
DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: LYON & LYON LLP, 633 WEST FIFTH STREET, SUITE 4700, LOS ANGELES, CA, 90071
NUMBER OF CLAIMS: 14
EXEMPLARY CLAIM: 1
LINE COUNT: 3352
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention includes a basic method for discovering the function of gene and their corresponding gene products relative to a specific biological process or physiological condition. The invention provides the ability to develop therapeutic and diagnostic agents using the information obtained from the practice of the basic method. In the method, the gene product of a selected polynucleotide is delivered to a mammal to provide an immune response. The polynucleotide sequences may express, in vivo by immunization of an animal, or in bacterial system or other known system for expression of a polynucleotide sequence. The sera resulting from immunization with the gene product contains antibodies to the gene product which are used in function determinative assays to determine the function of the gene sequence gene product relative to a biological process or physiological condition, typically a disease in a human. The information derived from the function determinative assay enables the discovery of novel genes and gene products and provides the ability to design and/or manufacture of therapeutic or diagnostic products based on the practice of the basic methodology of the invention.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L69 ANSWER 24 OF 64 USPATFULL on STN
ACCESSION NUMBER: 2003:291112 USPATFULL
TITLE: System for exsanguinous metabolic support of an organ or tissue
INVENTOR(S): Brasile, Lauren, Albany, NY, United States
PATENT ASSIGNEE(S): Breonics, Inc., Otisville, NY, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 6642045	B1	20031104
APPLICATION INFO.:	US 2000-547843		20000412 (9)

	NUMBER	DATE
PRIORITY INFORMATION:	US 1997-129257P	19970414 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: GRANTED
PRIMARY EXAMINER: Beisner, William H.
LEGAL REPRESENTATIVE: Heslin Rothenberg Farley & Mesiti P.C., Dias, Esq., Kathy Smith
NUMBER OF CLAIMS: 15
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 2 Drawing Figure(s); 2 Drawing Page(s)
LINE COUNT: 1790
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB An exsanguinous metabolic support system for maintaining an organ or

tissue at a near normal metabolic rate is disclosed. The system employs a warm perfusion solution capable of supporting the metabolism of the organ or tissue thereby preserving its functional integrity. The system also monitors parameters of the circulating perfusion solution, such as pH, temperature, osmolarity, flow rate, **vascular** pressure and partial pressure of respiratory gases, and regulates them to insure that the organ is maintained under near-physiologic **conditions**. Use of the system for long-term maintenance of organs for transplantation, for resuscitation and repair of organs having sustained warm ischemic damage, as a pharmaceutical delivery system and prognosticator of posttransplantation organ function is also disclosed.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L69 ANSWER 25 OF 64 USPATFULL on STN

ACCESSION NUMBER:	2003:102396 USPATFULL			
TITLE:	Remedies or preventives containing cyclopentenone compounds as the active ingredient			
INVENTOR(S):	Kobayashi, Eiji, Otsu, JAPAN Ohnogi, Hiromu, Muko, JAPAN Sagawa, Hiroaki, Kusatsu, JAPAN Tominaga, Takanari, Otsu, JAPAN Nishiyama, Eiji, Moriyama, JAPAN Koyama, Nobuto, Uji, JAPAN Ikai, Katsushige, Shiga, JAPAN Kato, Ikunoshin, Uji, JAPAN			
PATENT ASSIGNEE(S):	Takara Shuzo Co., Ltd., Kyoto, JAPAN (non-U.S. corporation)			
	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 6548543	B1	20030415	
	WO 2000010560		20000302	
APPLICATION INFO.:	US 2001-763244		20010220	(9)
	WO 1999-JP4323		19990810	
	NUMBER		DATE	
PRIORITY INFORMATION:	JP 1998-231659		19980818	
DOCUMENT TYPE:	Utility			
FILE SEGMENT:	GRANTED			
PRIMARY EXAMINER:	Weddington, Kevin E.			
LEGAL REPRESENTATIVE:	Browdy and Neimark, P.L.L.C.			
NUMBER OF CLAIMS:	4			
EXEMPLARY CLAIM:	1			
NUMBER OF DRAWINGS:	8 Drawing Figure(s); 8 Drawing Page(s)			
LINE COUNT:	1770			

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Remedies or preventives for diseases with a need for immunoregulation, diseases with a need for inhibition of inflammation, diseases with a need for regulation of tumor necrosis factor production, diseases with a need for regulation of fungal growth, diseases with a need for regulation of cell adhesion or disease with a deed for induction of heat-shock protein, which contain as the active ingredient at least one compound selected from among cyclopentenone derivatives represented by general formula [I], optically active isomers and salts thereof, wherein R.sub.1 and R.sub.2 are the same or different and each represents hydrogen, an aliphatic group, an aromatic group or an aromatic aliphatic group. ##STR1##

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L69 ANSWER 26 OF 64 USPATFULL on STN

ACCESSION NUMBER:	2003:67571 USPATFULL
TITLE:	Therapeutic agents
INVENTOR(S):	Enoki, Tatsuji, Otsu, JAPAN

Tomono, Jun, Muko, JAPAN
Koyama, Nobuto, Uji, JAPAN
Ikai, Katsushige, Koka-gun, JAPAN
Sagawa, Hiroaki, Kusatsu, JAPAN
Kato, Ikunoshin, Uji, JAPAN
PATENT ASSIGNEE(S): Takara Shuzo Co., Ltd., Kyoto, JAPAN (non-U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 6531148	B1	20030311	
	WO 9964424		19991216	
APPLICATION INFO.:	US 2001-719314		20010201	(9)
	WO 1999-JP3058		19990608	

	NUMBER	DATE
PRIORITY INFORMATION:	JP 1998-175295	19980609
	JP 1998-223723	19980724
	JP 1999-11639	19990120

DOCUMENT TYPE: Utility
FILE SEGMENT: GRANTED
PRIMARY EXAMINER: Page, Thurman K.
ASSISTANT EXAMINER: Evans, Charesse
LEGAL REPRESENTATIVE: Browdy and Neimark, P.L.L.C.
NUMBER OF CLAIMS: 23
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 12 Drawing Figure(s); 10 Drawing Page(s)
LINE COUNT: 2291
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB ##STR1##

Therapeutic or preventive agents for diseases requiring apoptosis induction, cancerous diseases, diseases requiring the inhibition of active oxygen production, those requiring the inhibition of nitrogen monoxide production, those requiring the inhibition of prostaglandin synthesis, those requiring the inhibition of synovial cell proliferation, those requiring the induction of heat shock protein production or those requiring the inhibition of α-glycosidase, which contain as the active ingredient compounds selected from among compounds represented by general formula (I), (wherein X and Y are each H or CH.sub.2OH, provided that when X is CH.sub.2OH, Y is H, while when X is H, Y is CH.sub.2OH), those represented by general formula (II), (wherein R is a residue obtained by freeing a compound having an SH group from the SH group) and salts of both; and foods, drinks, cosmetics and so on, containing compounds selected from among compounds of general formula (I), those of general formula (II) and salts of both.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L69 ANSWER 27 OF 64 BIOTECHNO COPYRIGHT 2004 Elsevier Science B.V. on STN
DUPLICATE
ACCESSION NUMBER: 2003:36667177 BIOTECHNO
TITLE: Fourteenth Annual Pezcoller Symposium: The novel dichotomy of immune interactions with tumors
AUTHOR: Hanahan D.; Lanzavecchia A.; Mihich E.
CORPORATE SOURCE: E. Mihich, Department of Pharmacology, Roswell Park Cancer Institute, Elm and Carlton Streets, Buffalo, NY 14263, United States.
SOURCE: Cancer Research, (01 JUN 2003), 63/11 (3005-3008)
CODEN: CNREA8 ISSN: 0008-5472
DOCUMENT TYPE: Journal; Conference Article
COUNTRY: United States
LANGUAGE: English
SUMMARY LANGUAGE: English
AN 2003:36667177 BIOTECHNO

AB The main focus of the Symposium was the fact that cell types of the innate and adaptive immune systems can have tumor-favoring as well as tumor antagonistic effects, both in a preventive and therapeutic mode. It was shown that macrophages (M.vphi.) and dendritic cells within a tumor exert tumor-favoring effects through the action of certain cytokines. Inflammatory reactions could favor the onset and growth of tumors. Dual immune functions were shown with CD4+ T cells and certain matrix metalloproteinase (MMP) activities favoring tumor progression and CD8+ T cells and certain **heat shock proteins** having antitumor action. Lack of antitumor action despite positive immune stimulation was also shown to depend on the existence of barriers to tumor infiltration by lymphocytes; remodeling of vasculature, e.g., by IFNγ-induced cytokines like MIG and IPIO, reversed this type of impediment. Certain CXC cytokines increased tumor progression, whereas others, particularly those induced by IFNγ, had the opposite effect; stromal-derived factor-1 and its receptor CXCR4 affected tumor propensity to metastasize in certain organs. Stromal-derived factor-1 induced MMP9, which in turn regulated the bioavailability of **vascular** endothelial growth factor and the cascade of its tumor-favoring effects, whereas granulocyte colony-stimulating factor decreased MMP9 and the consequences of its action. The effects of certain proinflammatory cytokines and **vascular** endothelial growth factor functions in angiogenesis and lymphoangiogenesis were also discussed. The favoring effects of fever-like thermal stress on the function of molecules instrumental in lymphoid cell adhesion to vessels and infiltration into sites of immune actions were described. The mechanisms involved in the development of immune memory and those conditioning Type I and CTL responses were also discussed. A number of presentations were concerned with laboratory studies aimed at developing clinical regimens with potential activity in the prevention or treatment of cancer. Prevention of Her2/neu breast cancer in transgenic mice was achieved by suitable regimens with IL12 combined with vaccines, including DNA-based vaccines **administered** in conjunction with electroporation. Vaccination with shared tumor antigen MUCI or cyclin B was discussed, and its clinical translation was described. The prevention of TRAMP prostate tumor in transgenic mice by anti-CTLA4 antibody plus vaccine was described, as was the translation of these regimens to the clinics. Clinical successes in melanoma patients using antimelanoma antigen antibodies in a therapeutic mode and precautions to be exerted in evaluating in vivo immune responses based on in vitro assays were emphasized. The symposium was concluded with an overall discussion focused on basic questions related to the capability of immunity to exert tumor-favoring or antitumor effects depending on **conditions** determined by both tumor and host functions.

L69 ANSWER 28 OF 64 PASCAL COPYRIGHT 2004 INIST-CNRS. ALL RIGHTS RESERVED. on STN

ACCESSION NUMBER:	2003-0497137 PASCAL
COPYRIGHT NOTICE:	Copyright .COPYRGT. 2003 INIST-CNRS. All rights reserved.
TITLE (IN ENGLISH):	Heme oxygenase-1 attenuates ischemia/reperfusion-induced apoptosis and improves survival in rat renal allografts
AUTHOR:	WAGNER Markus; CADETG Petra; RUF Rainer; MAZZUCCHELLI Luca; FERRARI Paolo; REDAELLI Claudio A.
CORPORATE SOURCE:	Department of Visceral and Transplantation Surgery, Department of Pathology, and Division of Nephrology and Hypertension, University of Bern, Bern, Switzerland
SOURCE:	Kidney international, (2003), 63(4), 1564-1573, 60 refs. ISSN: 0085-2538 CODEN: KDYIA5
DOCUMENT TYPE:	Journal
BIBLIOGRAPHIC LEVEL:	Analytic
COUNTRY:	United States
LANGUAGE:	English

AVAILABILITY: INIST-15906, 354000118563750410
AN 2003-0497137 PASCAL
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AB Background. Kidneys can be preserved only for a limited time without jeopardizing graft function and survival. Induction of **heat shock proteins** (HSPs) can protect against ischemia/reperfusion (I/R) injury. Therefore, we investigated whether the induction of the HSP, heme oxygenase-1 (HO-1), improves outcome following isotransplantation after an extended period of cold storage. Methods. Rats were subjected to heat preconditioning (HP; 42°C for 20 minutes). Kidneys harvested after 24 hours, were preserved in cold University of Wisconsin (UW) solution at 4° C for 45 hours and transplanted into bilateral nephrectomized rats. Cobalt protoporphyrin (CoPP) was **administered** in another group of animals in order to induce HO-1 pharmacologically, while other groups of animals received the HO-1 inhibitor, tin protophorphyrine (SnPP), following HP or CoPP. Results. Cold ischemia caused a complete attenuation of graft function within 3 days following transplantation and subsequent death of all animals, whereas HP protected graft function and five of nine rats survived for 3 weeks. HP inhibited the induction of osteopontin and induced the expression of HO-1, HSP 70 and 90, and the antiapoptotic factor Bcl-X.sub.L. Grafts exposed to HP were protected against structural I/R injuries as revealed by histologic assessment using a semiquantitative score. Furthermore, induction of apoptosis was attenuated and activation of caspase-3 was inhibited. Comparable results were observed after administration of CoPP, whereas SnPP inhibited the effects of HP and CoPP. Conclusion. HP or administration of CoPP induced both HO-1, preserved kidney graft function, and prevented postreperfusion apoptosis after cold preservation.

L69 ANSWER 29 OF 64 PASCAL COPYRIGHT 2004 INIST-CNRS. ALL RIGHTS RESERVED.
on STN
ACCESSION NUMBER: 2004-0108014 PASCAL
COPYRIGHT NOTICE: Copyright .COPYRGT. 2004 INIST-CNRS. All rights reserved.
TITLE (IN ENGLISH): Overexpression of rat heat shock protein 70 reduces neuronal injury after transient focal ischemia, transient global ischemia, or kainic acid-induced seizures. Comments
AUTHOR: TSUCHIYA Daisuke; SHWUHUEY HONG; MATSUMORI Yasuhiko; KAYAMA Takamasa; SWANSON Raymond A.; DILLMAN Wolfgang H.; JIALING LIU; PANTER S. Scott; WEINSTEIN Philip R.; MACDONALD R. Loch (comment.); KELLY Stephen (comment.); STEINBERG Gary K. (comment.); AWAD Issam A. (comment.); SELMAN Warren R. (comment.)
CORPORATE SOURCE: Department of Neurological Surgery, University of California, San Francisco, and Veterans Affairs Medical Center, San Francisco, California, United States; Department of Neurosurgery, Yamagata University School of Medicine, Yamagata, Japan; Department of Neurology, University of California, San Francisco, and Veterans Affairs Medical Center, San Francisco, California, United States; Department of Medicine, University of California, San Diego, La Jolla, California, United States
SOURCE: Neurosurgery, (2003), 53(5), 1179-1188, 37 refs. ISSN: 0148-396X CODEN: NRSRDY
DOCUMENT TYPE: Journal; Article; Commentary
BIBLIOGRAPHIC LEVEL: Analytic
COUNTRY: United States
LANGUAGE: English
AVAILABILITY: INIST-18396, 354000118758050200
AN 2004-0108014 PASCAL
CP Copyright .COPYRGT. 2004 INIST-CNRS. All rights reserved.
AB OBJECTIVE: Transgenic (Tg) mice overexpressing rat **heat shock protein** 70 (hsp70) demonstrated less infarction

than did wild-type (WT) littermates after permanent focal cerebral ischemia. The purpose of this study was to determine whether neuronal injury and apoptosis were reduced in hsp70 Tg mice after transient focal ischemia. The effects of hsp70 overexpression were also evaluated after transient global ischemia or kainic acid (KA)-induced seizures, to verify the results in other excitotoxic stress models. METHODS: Transient focal ischemia was produced with middle cerebral artery occlusion via intraluminal suture cannulation. Infarction volumes were assessed 24 hours after 30 minutes of middle cerebral artery occlusion. Transient global ischemia was produced with 25 minutes of bilateral common carotid artery occlusion. KA (30 mg/kg) was **administered** subcutaneously, and seizure activity was evaluated. The number of eosinophilic neurons was assessed in the CA1 region 72 hours after bilateral common carotid artery occlusion and in the CA3 region 24 hours after KA administration. RESULTS: The infarction volume after transient middle cerebral artery occlusion was significantly smaller in hsp70 Tg mice than in WT mice (9.1 ± 5.7 mm.sup.3 versus 22.4 ± 16.8 mm.sup.3, P < 0.05). The number of eosinophilic neurons in the CA1 area after bilateral common carotid artery occlusion and in CA3 after KA injection was significantly lower in hsp70 Tg mice than in WT mice (949.1 ± 1095.5 versus 2406.9 ± 1380.3, P < 0.05, and 33.8 ± 45.3 versus 119.4 ± 112.1, P < 0.05, respectively). Fewer terminal deoxynucleotidyl transferase-mediated biotinylated deoxyuridine triphosphate nick end-labeling-positive cells were observed in hsp70 Tg mice than in WT mice in each model. CONCLUSION: The results demonstrate that overexpression of hsp70 reduces neuronal injury after ischemia and seizures. The reduction in the number of terminal deoxynucleotidyl transferase-mediated biotinylated deoxyuridine triphosphate nick end-labeling-positive cells in hsp70 Tg mice suggests that hsp70 overexpression might reduce apoptotic cell death.

L69 ANSWER 30 OF 64 BIOTECHDS COPYRIGHT 2004 THOMSON DERWENT/ISI on STN
ACCESSION NUMBER: 2003-12940 BIOTECHDS
TITLE: New polypeptide which negatively regulates binding of heat shock protein to a substrate or induces ubiquitylation of a heat shock bound substrate, useful for identifying an inhibitor of the polypeptide;
vector expression in Escherichia coli for recombinant protein production and disease therapy
AUTHOR: PATTERSON W C; BALLINGER C A
PATENT ASSIGNEE: UNIV TEXAS SYSTEM
PATENT INFO: US 2002177212 28 Nov 2002
APPLICATION INFO: US 2001-13939 7 Dec 2001
PRIORITY INFO: US 2001-13939 7 Dec 2001; US 1999-134433 17 May 1999
DOCUMENT TYPE: Patent
LANGUAGE: English
OTHER SOURCE: WPI: 2003-298777 [29]
AN 2003-12940 BIOTECHDS
AB DERWENT ABSTRACT:
NOVELTY - A polypeptide (I) which negatively regulates binding of **heat shock protein** (Hsp) to a substrate or induces ubiquitylation of a heat shock bound substrate, has a sequence of 303, 304 or 289 amino acids, and is encoded by a nucleic acid that hybridizes to a sequence of 1286, 1218 or 1225 nucleotides, or a human carboxy terminus of a Hsc70 interacting protein genomic nucleotide sequence, is new.

DETAILED DESCRIPTION - An isolated polypeptide (I) which negatively regulates binding of a **heat shock protein** (Hsp) to a substrate or induces ubiquitylation of a heat shock bound substrate, comprises: (i) an amino acid sequence (S1) of 303, 304 or 289 amino acids, given in the specification; (ii) a sequence (S2) having greater than about 40 % sequence identity to (S1); or (iii) a polypeptide comprising amino acids 1 - 197 of (S2), encoded by a nucleic acid that hybridizes to a nucleic acid or a nucleic acid complement of a sequence (S3) comprising 1286, 1218, or 1225 nucleotides, or a human carboxy terminus of Hsc70 interacting protein (CHIP) genomic nucleotide sequence,

given in the specification, under hybridization **conditions** (HC) of 0.015 M NaCl/0.0015 M sodium citrate (SSC) and about 0.1 % sodium dodecyl sulfate (SDS) at about 50 - 65 degreesC. INDEPENDENT CLAIMS are also included for the following: (1) a nucleic acid fragment (II) capable of hybridizing to (S3) or its complement under HC; (2) a nucleic acid vector containing (II); (3) a host cell comprising (II); (4) an isolated nucleic acid fragment comprising (S3) or its complement, or a nucleic acid sequence (S4) with 60 % nucleic acid identity to (S3) or its complement; (5) expressing (M) a nucleic acid fragment that encodes a polypeptide, the presence of which is associated with a negative regulation of a **heat shock protein** or ubiquitylation of a heat shock bound substrate, comprising expressing the nucleic acid fragment in a cultured host cell transformed with an expression vector comprising the nucleic acid fragment operably linked to control sequences recognized by the host cell; (6) producing a recombinant polypeptide; (7) inhibiting a nucleic acid that encodes a polypeptide that negatively regulates binding of a **heat shock protein** to a substrate or induces ubiquitylation of a heat shock bound substrate in a mammal, comprising **administering** to a mammal a composition comprising an amount of an inhibitor to an isolated nucleic acid fragment having (S4) or its complement; and (8) an inhibitory composition (C) comprising an amount of an inhibitor to the isolated polypeptide which negatively regulates binding of Hsp to a substrate effective to immunize or treat a mammal for a neoplastic **disease**, ischemic **disease** or a **disease** characterized by inflammation.

BIOTECHNOLOGY - Preparation: (I) Is produced by: (a) providing an expression vector that comprises a nucleic acid fragment having (S4) or its complement, operably linked to control sequences recognized by a host cell; (b) transforming the host cell with the expression vector; and (c) culturing the transformed cell under **conditions** that allow expression of the recombinant polypeptide encoded by the nucleic acid fragment. Preferred Polypeptide: (I) Interacts with a S5a proteasome subunit of an ubiquitin-proteasome degradative pathway. A U-box domain of (I) interacts with a S5a proteasome subunit. (I) Is a recombinant polypeptide. (I) Has a molecular weight as determined by sodium dodecyl sulfate (SDS) polyacrylamide gel electrophoresis (PAGE) of about 30 - 40 kD. Preferred Nucleic Acid: The nucleic acid fragment encodes a portion of (I). Preferred Vector: The vector is an expression vector capable of producing a portion of (I). Preferred Cell: The host cell is prokaryotic or eukaryotic cell. Preferred Method: The prokaryotic host cell is a gram negative or gram positive organism. The host cell is an Escherichia coli cell. (M) further involves recovering the polypeptide from the host cell. Preferred Composition: (I) is in combination with a carrier.

ACTIVITY - Immunosuppressive; Antiinflammatory; Cardiant; Cerebroprotective; Cytostatic; Vasodilator; Vasotropic. No biological data is given.

MECHANISM OF ACTION - Binding of **heat shock protein** to substrate negative regulator; Ubiquitylation of heat shock bound substrate inducer (claimed).

USE - (I) Is useful for negatively regulating binding of Hsp, such as, Hsc70, Hsp70 or Hsp90 to a substrate or for inducing ubiquitylation of a heat shock bound substrate. (I) Is useful for identifying an inhibitor of (I), by: (a) incubating (I) with a compound under **conditions** that promote the negative regulating activity of the polypeptide or ubiquitylation activity of the polypeptide when the compound is not present; and (b) determining if the negative regulating activity or ubiquitylation activity of the polypeptide is reduced relative to the negative regulating activity or ubiquitylation activity of the polypeptide in the absence of the compound. (C) Is useful for inhibiting (I) in a mammal. (C) Is therapeutically effective for a neoplastic **disease**, ischemic **disease** or **disease** characterized by inflammation (claimed). (C) Is useful for treating, inhibiting or preventing neoplastic **diseases** such as cancer or lymphoma, ischemic **diseases** such as stroke, **vascular disease**, or myocardial infarction, or a

disease characterized by inflammation, which includes infections and autoimmune **diseases**.

ADMINISTRATION - Administration is through local, systemic, parenteral, subcutaneous, intramuscular, or oral routes. No dosage is given.

EXAMPLE - cDNA cloning of a human, mouse, and Drosophila carboxy terminus of Hsc70 (**heat shock protein**) interacting protein (CHIP) was carried out as follows. A nucleic acid fragment corresponding to nucleotides 721 - 1150 of the human cyclophilin 40 (CyP-40) cDNA was radiolabeled with (alpha-32P)dCTP, and used to screen a phage library of human heart DNA in the vector lambdagt11. Phage colonies were grown on agarose and transferred to nitrocellulose membranes. Phage colonies that hybridized preferentially under low-stringency **conditions** (0.2 x saline sodium citrate (SSC), 0.1 % sodium dodecyl sulfate (SDS) at 42 degrees Centigrade) were analyzed and characterized. A total of 12 colonies were characterized by plaque isolation, amplification and sequencing, and it was determined that eight colonies contained human CyP-40 cDNA sequences, and four colonies encoded a new cDNA having no sequence identity to known genes available in GenBank (RTM). The new cDNA was analyzed using Basic Local Alignment Search Tool (BLAST) and GenBank (RTM) databases. Human expressed sequence tag (EST) sequences found to be identical to the cDNA sequence of the new cDNA obtained by phage screening were Clone ID Nos: 548268, 177869, and 647520. Clones 548268 and 177869 contained polyadenylated sequence at the 3' end. The 5' end of the cDNA was defined by 5' rapid amplification of cDNA ends using human heart mRNA and primers designed on the basis of EST sequences P1 and P2. Products of these reactions, as well as plasmids containing the EST fragments, were sequenced and a single contiguous human cDNA sequence was assembled. Homologous mouse and Drosophila cDNAs (comprising a sequence of 1218 and 1225 nucleotides fully defined in the specification, respectively) were identified in a similar manner, based on EST clones ID Nos. 525111 and 546365 (mouse) and clone ID Number LD16049 (Drosophila). Sequence comparisons were made using GeneWorks 2.5.1 (RTM) software using the CLUSTRAL (RTM) alignment default parameters. gctgtaagctcgctgcagat (P1) gcctcatcatagctctccatctc (P2)(50 pages)

L69 ANSWER 31 OF 64 BIOTECHDS COPYRIGHT 2004 THOMSON DERWENT/ISI on STN
ACCESSION NUMBER: 2002-17101 BIOTECHDS
TITLE: Inhibiting the generation of active thrombin on the surface of a cell of a mammal for treating thrombotic disorders, involves producing an endoplasmic reticulum resident chaperone protein in the cell;
recombinant protein production by vector-mediated gene transfer and expression in host cell
AUTHOR: AUSTIN R C; CHAN A K C; BERRY L R
PATENT ASSIGNEE: AUSTIN R C; CHAN A K C; BERRY L R
PATENT INFO: US 2002039791 4 Apr 2002
APPLICATION INFO: US 2000-834760 14 Apr 2000
PRIORITY INFO: US 2001-834760 12 Apr 2001
DOCUMENT TYPE: Patent
LANGUAGE: English
OTHER SOURCE: WPI: 2002-443185 [47]
AN 2002-17101 BIOTECHDS
AB DERWENT ABSTRACT:

NOVELTY - Inhibiting (M1) the generation of active thrombin on the surface of a cell of a mammal comprising producing an endoplasmic reticulum (ER) resident chaperone protein (P1) in the cell, is new.

DETAILED DESCRIPTION - An INDEPENDENT CLAIM is included for identifying (M2) a compound useful in the treatment or prevention of a thrombotic **disease** or **condition**, which involves contacting a cell that expresses (P1) or that is capable of expressing (P1), with the compound, and detecting the functional effect of the compound on (P1), where an increase in the expression or activity of (P1) in the cell indicates that the compound is useful.

WIDER DISCLOSURE - Disclosed are: (1) use of cells e.g. endothelial

cell lines over-expressing GRP78/BiP, as model systems to understand the factors which mediate cell surface thrombin generation in endothelial cells; and (2) diagnostic and therapeutic kits.

BIOTECHNOLOGY - Preferred Method: (P1) is Glucose Regulated Protein 78, also known as immunoglobulin heavy chain-binding protein (GRP78/BiP), GRP94, GRP72, Calreticulin, Calnexin, Protein disulfide isomerase, cis/trans-Prolyl isomerase or **heat shock protein** (HSP)-47. Production of (P1) within the cell results in a decrease in the level of tissue factor procoagulant activity on the surface of the cell present within atherosclerotic plaque within the mammal. A polynucleotide encoding (P1), operably linked to a promoter, is introduced into the cell, such that (P1) is produced. The polynucleotide is introduced into the cell using a viral vector e.g. adenoviral vector or non-viral vector, as naked deoxyribonucleic acid (DNA) or using liposome-mediated transfection. Alternately, (P1) is produced by **administering** a compound e.g. cytokine that induces the expression or activation of endogenous (P1).

ACTIVITY - Thrombolytic.

MECHANISM OF ACTION - Induces expression or activation of ER resident chaperone protein in a cell without inducing ER stress; inhibitor of active thrombin generation on cell surface (claimed). Total amidolytic activity of thrombin generated on T24/83 cell surfaces was measured as described in Ling et al. (1995) Pediatr. Res. 37:373-378, Chan et al. (1998) Lung Cell. Mol. Physiol. 18:L914-L921. T24/83 cell monolayers were incubated for 3 minutes with 100 mul of ABS buffer and 200 mul defibrinated plasma, in the presence or absence of 10% activated partial thromboplastin time (APTT) reagent. At various times following the addition of 100 mul of 0.04 M CaCl2 in ABS buffer, 25 mul aliquots of the reaction mixture on the surface of the cells were removed and mixed with 475 mul of 0.005 M Na2 ethylenediaminetetraacetic acid (EDTA) on ice. 25 mul of each EDTA sample were then mixed with 775 mul of 0.00016 M S-2238 in buffer and heated to 37degreesC for 10 minutes prior to termination of the amidolytic reaction with 200 mul of 50% acetic acid. The absorbance at 405 nm was measured and the concentration of total thrombin determined by comparing results to a standard curve generated with purified thrombin in S-2238. In control plasma, after the addition of calcium, the concentration of total thrombin generated on the cell surface of T24/83 cells overexpressing GRP78/BiP was significantly less after 2 minutes, relative to wild-type or vector-transfected cells (p lesser than 0.001). The concentration of free thrombin generated on the surface of T24/83 cells overexpressing GRP78/BiP was negligible for all time points examined, up to 25 minutes. In contrast to the GRP78/BiP overexpressing cells, free thrombin levels generated on the surface wild-type or vector-transfected T24/83 cells were significantly higher than 110+/-16 and 131+/-2 nM, respectively, by 4 minutes after the addition of calcium (p lesser than 0.001). Consistent with these findings, both prothrombin consumption and thrombin-inhibitor complexes were significantly reduced in the GRP78/BiP overexpressing cells, compared with wild-type or vector-transfected cells.

USE - M1 is useful for inhibiting the generation of active thrombin on the surface of a cell (e.g. endothelial cell, smooth muscle cell, macrophage or monocyte) of a mammal, and thus useful for preventing or treating a thrombotic **disease** or **condition** in a mammal which has had myocardial infarction, angioplasty or stentin, cranial radiation or **vascular** surgery. M2 is useful for identifying a compound which is useful for treating or preventing a thrombotic **disease** in a mammal (claimed).

ADMINISTRATION - 0.1-100 mg/patient/day, preferably 0.1-10 mg/patient/day of the compound identified by M2 is **administered** parentally, topically, orally or locally by an aerosol or transdermal route.

EXAMPLE - To obtain cells stably expressing Glucose Regulated Protein 78, also known as immunoglobulin heavy chain-binding protein (GRP78/BiP),T24/83 cells were transfected with either the mammalian cell expression vector pcDNA3.1(+) or pcDNA3.1(+) containing the open reading frame of human GRP78/BiP. The latter vector was obtained by amplifying

the complementary deoxyribonucleic acid (cDNA) encoding the open-reading frame of human GRP78/BiP (approximately 1.95 kb) by reverse transcriptase-polymerase chain reaction (RT-PCR) using total ribonucleic acid (RNA) from primary human umbilical vein endothelial cells (HUVEC). GRP78/BiP cDNA was generated using SuperScript ribonuclease H (RNase H) reverse transcriptase and a primer complimentary to a sequence in the 3'-untranslated region of the human GRP78/BiP messenger RNA (mRNA) transcript (i). For PCR amplification, primer (ii) contained a Kozak consensus sequence prior to the initiating ATG and the terminal HindIII restriction site, and primer (iii) contained a terminal XhoI restriction site adjacent to the authentic termination codon after GRP78/BiP cDNA. All samples were subjected to amplification in a DNA thermal cycler 480. The amplified GRP78/BiP cDNA was separated on a 0.8% agarose-TBE gel containing ethidium bromide, purified from the agarose gel using the QIAEX gel extraction kit. The ligation mixture was then used to transform competent DH5alpha cells. Plasmid DNA was isolated from transformed cells using QIAEX miniprep kit, digested with HindIII and XhoI, and the GRP78/BiP cDNA insert purified from agarose. GRP78/BiP cDNA insert was ligated into the HindIII/XhoI-site of the mammalian expression vector pcDNA3.1(+) to produce the recombinant plasmid, pcDNA3.1(+)-GRP78/BiP. Authenticity of the GRP78/BiP cDNA sequence was confirmed by fluorescence-based double stranded DNA sequencing. AB 10230, 5'-TATTACAGCACTAGCAGATCAGTG-3' (i); AB10231 5'-CTTAAGCTTGCCACCATGAAGCTCTCCCTGGTGGCCGCG-3' (ii); and AB10232 5'-AGGCCTCGAGCTACAACTCATCTTTTTCTGCTGT-3' (iii).(30 pages)

L69 ANSWER 32 OF 64 USPATFULL on STN DUPLICATE 4

ACCESSION NUMBER: 2002:22153 USPATFULL
TITLE: Organ chamber for exsanguinous metabolic support system
INVENTOR(S): Brasile, Lauren, Albany, NY, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2002012988	A1	20020131
	US 6582953	B2	20030624
APPLICATION INFO.:	US 2001-849618	A1	20010504 (9)

RELATED APPLN. INFO.: Continuation-in-part of Ser. No. US 2000-547843, filed on 12 Apr 2000, PENDING

	NUMBER	DATE
PRIORITY INFORMATION:	WO 2000-US9894	20000413
	US 1999-129257P	19990414 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: HESLIN ROTHENBERG FARLEY & MESITI PC, 5 COLUMBIA CIRCLE, ALBANY, NY, 12203
NUMBER OF CLAIMS: 40
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 7 Drawing Page(s)
LINE COUNT: 2230

AB An exsanguinous metabolic support system for maintaining an organ or tissue at a near normal metabolic rate is disclosed. The system employs an organ chamber comprising a container and a support member adapted to inhibit movement of the organ within the container during perfusion and/or transport. The organ chamber additionally comprises a conduit for receiving venous outflow of perfusion solution and preventing its contact with the outer surfaces of the organ. A conduit for receiving organ product enables the collection of organ product from a functional organ during perfusion. Use of the organ chamber supports de novo or continued synthesis of constituents necessary for long-term maintenance of organs for transplantation, for resuscitation and active repair of organs that have sustained warm ischemic damage, and for transportation of isolated organs is also disclosed.

L69 ANSWER 33 OF 64 IFIPAT COPYRIGHT 2004 IFI on STN

AN	10238976 IFIPAT;IFIUDB;IFICDB
TITLE:	VASCULAR ENDOTHELIAL GROWTH FACTOR 2
INVENTOR(S):	Cao; Liang, Bethesda, MD, US Hu; Jing-Shan, Mountain View, CA, US Rosen; Craig A., Laytonsville, MD, US
PATENT ASSIGNEE(S):	Human Genome Sciences, Inc., Rockville, MD
AGENT:	HUMAN GENOME SCIENCES INC, 9410 KEY WEST AVENUE, ROCKVILLE, MD, 20850

	NUMBER	PK	DATE
PATENT INFORMATION:	US 2002182683	A1	20021205
APPLICATION INFORMATION:	US 2002-60523		20020201

	APPLN. NUMBER	DATE	GRANTED PATENT NO. OR STATUS
CONTINUATION of:	US 1999-257918	19990226	ABANDONED
CONTINUATION of:	US 2000-618451	20000718	ABANDONED
DIVISION of:	US 1994-207550	19940308	ABANDONED
DIVISION of:	US 1997-824996	19970327	5935820
FAMILY INFORMATION:	US 2002182683	20021205	
	US 5935820		

DOCUMENT TYPE:	Utility Patent Application - First Publication
FILE SEGMENT:	CHEMICAL APPLICATION
NUMBER OF CLAIMS:	20 89 Figure(s).

DESCRIPTION OF FIGURES:

FIGS. 1A-D (FIG. 1A shows the first portions of the polynucleotide sequence encoding VEGF2 and the amino acid sequence for VEGF2, and FIGS. 1B, 1C and 1D, respectively continue with the sequential portions of each sequence began in FIG. 1A) collectively depict the polynucleotide sequence (SEQ ID NO:1) which encodes VEGF2, and the corresponding amino acid sequence (SEQ ID NO:2) for the VEGF2 polypeptide comprising 350 amino acid residues of which approximately the first 24 amino acids represent the leader sequence. The standard one-letter codes are utilized to depict the amino acid residues encoded by the polynucleotide triplets.

FIGS. 2A-B collectively depict polypeptide sequences in alignment and show the alignment of VEGF2 with the other growth factor PDGF alpha, PDGF beta, and VEGF. FIG. 2A depicts Nterminal portions of the polypeptide sequences and FIG. 2A continues with C-terminal portions of the polypeptide sequences. The four lines in each comparative row depict, respectively, the PDGF alpha polypeptide sequence (SEQ ID NO:7), the PDGF beta polypeptide sequence (SEQ ID NO:8), the VEGF polypeptide sequence (SEQ ID NO:9) and the VEGF2 polypeptide sequence. The amino acid residues are illustrated in FIGS. 2A and 2B by the standard one-letter codes.

FIG. 3 shows, in table-form, the percent homology between PDGF alpha, PDGF beta, VEGF and VEGF2.

FIG. 4 shows the presence of mRNA for VEGF2 in breast tumor cell lines.

FIG. 5 depicts the results of a Northern blot analysis of VEGF2 in human adult tissues.

FIG. 6 shows the results of running VEGF2 and SDS-PAGE gel after in vitro transcription/translation. The full length and partial VEGF2 cDNA were transcribed and translated in a coupled reaction in the presence of 35S-methionine. The translated products were analyzed by 4-20% gradient SDS PAGE and exposed to X-ray film.

In accordance with one aspect of the present invention, there is provided an isolated nucleic acid (polynucleotide) which encodes for the mature polypeptide having the deduced amino acid sequence of SEQ ID NO:2 or for the mature polypeptide encoded by the cDNA of the clone deposited as ATCC Deposit No. 75698, on Mar. 4, 1994, with ATCC, 10801 University Boulevard, Manassas, Va. 20110-2209. Since the strain referred to is being maintained under the terms of the Budapest Treaty, it will be made available to a patent office signatory to the Budapest Treaty. If a patent should issue which is directed to the present

invention, upon the issuance of such a patent the deposited strain of ATCC 75698 will be irrevocably and without restriction released to the public, excepting for those restrictions permitted by enforcement of the patent.

A polynucleotide encoding a polypeptide of the present invention may be obtained from early stage human embryo (week 8 to 9) osteoclastomas, adult heart or several breast cancer cell lines. The polynucleotide of this invention was discovered in a cDNA library derived from early stage human embryo week 9. It is structurally related to the VEGF/PDGF family. It contains an open reading frame encoding a protein of about 350 amino acid residues of which approximately the first 24 amino acid residues are likely to be leader sequence such that the mature protein comprises 326 amino acids, and which protein exhibits the highest homology to **vascular** endothelial growth factor (30% identity), followed by PDGF alpha (23%) and PDGF beta (22%), (see FIG. 3). It is particularly important that all eight cysteines are conserved within all four members of the family (see boxed areas of FIG. 2). In addition, the signature for the PDGF/VEGF family, PXCVXXXRCXGCCN, (SEQ ID NO:3) is conserved in VEGF2 (see FIG. 2). The homology between VEGF2, VEGF and the two PDGFs is at the protein sequence level. No nucleotide sequence homology can be detected, and therefore, it would be difficult to isolate the VEGF2 through simple approaches such as low stringency hybridization.

The polynucleotide of the present invention may be in the form of RNA or in the form of DNA, which DNA includes cDNA, genomic DNA, and synthetic DNA. The DNA may be double-stranded or single-stranded, and if single stranded may be the coding strand or non-coding (anti-sense) strand. The coding sequence which encodes the mature polypeptide may be identical to the coding sequence shown in SEQ ID NO:1 or that of the deposited clone or may be a different coding sequence which coding sequence, as a result of the redundancy or degeneracy of the genetic code, encodes the same, mature polypeptide as the DNA of SEQ ID NO:1 or the deposited cDNA.

The polynucleotide which encodes for the mature polypeptide of FIG. 1 or for the mature polypeptide encoded by the deposited cDNA may include: only the coding sequence for the mature polypeptide; the coding sequence for the mature polypeptide and additional coding sequence such as a leader or secretory sequence or a proprotein sequence; the coding sequence for the mature polypeptide (and optionally additional coding sequence) and non-coding sequence, such as introns or non-coding sequence 5' and/or 3' of the coding sequence for the mature polypeptide.

Thus, the term "polynucleotide encoding a polypeptide" encompasses a polynucleotide which includes only coding sequence for the polypeptide as well as a polynucleotide which includes additional coding and/or non-coding sequence.

The present invention further relates to variants of the hereinabove described polynucleotides which encode for fragments, analogs and derivatives of the polypeptide having the deduced amino acid sequence of FIG. 1 or the polypeptide encoded by the cDNA of the deposited clone. The variant of the polynucleotide may be a naturally occurring allelic variant of the polynucleotide or a non-naturally occurring variant of the polynucleotide.

Thus, the present invention includes polynucleotides encoding the same mature polypeptide as shown in FIG. 1 or the same mature polypeptide encoded by the cDNA of the deposited clone as well as variants of such polynucleotides which variants encode for an fragment, derivative or analog of the polypeptide of FIG. 1 or the polypeptide encoded by the cDNA of the deposited clone. Such nucleotide variants include deletion variants, substitution variants and addition or insertion variants.

As hereinabove indicated, the polynucleotide may have a coding sequence which is a naturally occurring allelic variant of the coding sequence shown in SEQ ID NO:1 or of the coding sequence of the deposited clone. As known in the art, an allelic variant is an alternate form of a polynucleotide sequence which have a substitution, deletion or addition of one or more nucleotides, which does not substantially alter the function of the encoded polypeptide.

The present invention also includes polynucleotides, wherein the coding sequence for the mature polypeptide may be fused in the same reading frame to a polynucleotide which aids in expression and secretion of a polypeptide from a host cell, for example, a leader sequence which functions as a secretory sequence for controlling transport of a polypeptide from the cell. The polypeptide having a leader sequence is a preprotein and may have the leader

sequence cleaved by the host cell to form the mature form of the polypeptide. The polynucleotides may also encode for a proprotein which is the mature protein plus additional 5' amino acid residues. A mature protein having a prosequence is a proprotein and is an inactive form of the protein. Once the prosequence is cleaved an active mature protein remains.

Thus, for example, the polynucleotide of the present invention may encode for a mature protein, or for a protein having a prosequence or for a protein having both a prosequence and presequence (leader sequence).

The polynucleotides of the present invention may also have the coding sequence fused in frame to a marker sequence which allows for purification of the polypeptide of the present invention. The marker sequence may be a hexa-histidine tag supplied by a pQE-9 vector to provide for purification of the mature polypeptide fused to the marker in the case of a bacterial host, or, for example, the marker sequence may be a hemagglutinin (HA) tag when a mammalian host, e.g. COS-7 cells, is used. The HA tag corresponds to an epitope derived from the influenza hemagglutinin protein (Wilson, I., et al., Cell, 37:767 (1984)).

The present invention further relates to polynucleotides which hybridize to the hereinabove-described sequences if there is at least 50% and preferably 70% identity between the sequences. The present invention particularly relates to polynucleotides which hybridize under stringent **conditions** to the hereinabovedescribed polynucleotides . As herein used, the term "stringent ***conditions*** " means hybridization will occur only if there is at least 95% and preferably at least 97% identity between the sequences. The polynucleotides which hybridize to the hereinabove described polynucleotides in a preferred embodiment encode polypeptides which retain substantially the same biological function or activity as the mature polypeptide encoded by the cDNA of SEQ ID NO:2 or the deposited cDNA.

The deposit(s) referred to herein will be maintained under the Budapest Treaty on the International Recognition of the Deposit of Microorganisms for the purposes of Patent Procedure. These deposits are provided merely as a convenience and are not an admission that a deposit is required under 35 U.S.C. section 112. The sequence of the polynucleotides contained in the deposited materials, as well as the amino acid sequence of the polypeptides encoded thereby, are incorporated herein by reference and are controlling in the event of any conflict with the description of sequences herein. A license may be required to make, use or sell the deposited materials, and no such license is hereby granted.

DESCRIPTION OF FIGURES:

The present invention further relates to a VEGF2 polypeptide which has the deduced amino acid sequence of SEQ ID NO:2 or which has the amino acid sequence encoded by the deposited cDNA, as well as fragments, analogs and derivatives of such polypeptide.

The terms "fragment," "derivative" and "analog" when referring to the polypeptide of SEQ ID NO:2 or that encoded by the deposited cDNA, means a polypeptide which retains essentially the same biological function or activity as such polypeptide. Thus, an analog includes a proprotein which can be activated by cleavage of the proprotein portion to produce an active mature polypeptide.

The polypeptide of the present invention may be a recombinant polypeptide, a natural polypeptide or a synthetic polypeptide, preferably a recombinant polypeptide.

The fragment, derivative or analog of the polypeptide of SEQ ID NO:2 or that encoded by the deposited cDNA may be (i) one in which one or more of the amino acid residues are substituted with a conserved or non-conserved amino acid residue (preferably a conserved amino acid residue) and such substituted amino acid residue may or may not be one encoded by the genetic code, or (ii) one in which one or more of the amino acid residues includes a substituent group, or (iii) one in which the mature polypeptide is fused with another compound, such as a compound to increase the half-life of the polypeptide (for example, polyethylene glycol), or (iv) one in which the additional amino acids are fused to the mature polypeptide, such as a leader or secretory sequence or a sequence which is employed for purification of the mature polypeptide or a proprotein sequence. Such fragments, derivatives and analogs are deemed to be within the scope of those skilled in the art from the teachings herein.

The polypeptides and polynucleotides of the present invention are preferably

provided in an isolated form, and preferably are purified to homogeneity.
The term "isolated" means that the material is removed from its original environment (e.g., the natural environment if it is naturally occurring). For example, a naturally-occurring polynucleotide or polypeptide present in a living animal is not isolated, but the same polynucleotide or DNA or polypeptide, separated from some or all of the coexisting materials in the natural system, is isolated. Such polynucleotide could be part of a vector and/or such polynucleotide or polypeptide could be part of a composition, and still be isolated in that such vector or composition is not part of its natural environment.
The present invention also relates to vectors which include polynucleotides of the present invention, host cells which are genetically engineered with vectors of the invention and the production of polypeptides of the invention by recombinant techniques.
Host cells are genetically engineered (transduced or transformed or transfected) with the vectors of this invention which may be, for example, a cloning vector or an expression vector. The vector may be, for example, in the form of a plasmid, a viral particle, a phage, etc. The engineered host cells can be cultured in conventional nutrient media modified as appropriate for activating promoters, selecting transformants or amplifying the VEGF2 genes. The culture conditions, such as temperature, pH and the like, are those previously used with the host cell selected for expression, and will be apparent to the ordinarily skilled artisan.
The polynucleotide of the present invention may be employed for producing a polypeptide by recombinant techniques. Thus, for example, the polynucleotide sequence may be included in any one of a variety of expression vehicles, in particular vectors or plasmids for expressing a polypeptide. Such vectors include chromosomal, nonchromosomal and synthetic DNA sequences, e.g., derivatives of SV40; bacterial plasmids; phage DNA; yeast plasmids; vectors derived from combinations of plasmids and phage DNA, viral DNA such as vaccinia, adenovirus, fowl pox virus, and pseudorabies. However, any other plasmid or vector may be used as long as it is replicable and viable in the host.
As hereinabove described, the appropriate DNA sequence may be inserted into the vector by a variety of procedures. In general, the DNA sequence is inserted into an appropriate restriction endonuclease sites by procedures known in the art. Such procedures and others are deemed to be within the scope of those skilled in the art.
The DNA sequence in the expression vector is operatively linked to an appropriate expression control sequence(s) (promoter) to direct mRNA synthesis. As representative examples of such promoters, there may be mentioned: LTR or SV40 promoter, the E. coli. lac or trp, the phage lambda PL promoter and other promoters known to control expression of genes in prokaryotic or eukaryotic cells or their viruses. The expression vector also contains a ribosome binding site for translation initiation and a transcription terminator. The vector may also include appropriate sequences for amplifying expression.
In addition, the expression vectors preferably contain a gene to provide a phenotypic trait for selection of transformed host cells such as dihydrofolate reductase or neomycin resistance for eukaryotic cell culture, or such as tetracycline or ampicillin resistance in E. coli.
The vector containing the appropriate DNA sequence as herein above described, as well as an appropriate promoter or control sequence, may be employed to transform an appropriate host to permit the host to express the protein. As representative examples of appropriate hosts, there may be mentioned: bacterial cells, such as E. coli, Salmonella typhimurium Streptomyces; fungal cells, such as yeast; insect cells, such as Drosophila and Sf9; animal cells such as CHO, COS or Bowes melanoma; plant cells, etc. The selection of an appropriate host is deemed to be within the scope of those skilled in the art from the teachings herein.
More particularly, the present invention also includes recombinant constructs comprising one or more of the sequences as broadly described above. The constructs comprise a vector, such as a plasmid or viral vector, into which a sequence of the invention has been inserted, in a forward or reverse orientation. In a preferred aspect of this embodiment, the construct further comprises regulatory sequences, including, for example, a promoter, operably linked to the sequence. Large numbers of suitable vectors and promoters are

known to those of skill in the art, and are commercially available. The following vectors are provided by way of example. Bacterial: pQE70, pQE-9 (Qiagen), pBs, phagescript, PsiX174, pBluescript SK, pBsKS, pNH8a, pNH16a, pNH18a, pNH46a (Stratagene); pTrc99A, pKK223-3, pKK233-3, pDR540, PRIT5 (Pharmacia). Eukaryotic: pWLneo, pSV2cat, pOG44, pXT1, pSG (Stratagene) pSVK3, pBPV, pMSG, pSVL (Pharmacia). However, any other plasmid or vector may be used as long as they are replicable and viable in the host.

Promoter regions can be selected from any desired gene using CAT (chloramphenicol transferase) vectors or other vectors with selectable markers. Two appropriate vectors are pKK232-8 and pCM7. Particular named bacterial promoters include lacI, lacZ, T3, T7, gpt, lambda PR, PL and trp. Eukaryotic promoters include CMV immediate early, HSV thymidine kinase, early and late SV40, LTRs from retrovirus, and mouse metallothionein-I. Selection of the appropriate vector and promoter is well within the level of ordinary skill in the art.

In a further embodiment, the present invention relates to host cells containing the above-described construct. The host cell can be a higher eukaryotic cell, such as a mammalian cell, or a lower eukaryotic cell, such as a yeast cell, or the host cell can be a prokaryotic cell, such as a bacterial cell. Introduction of the construct into the host cell can be effected by calcium phosphate transfection, DEAE-Dextran mediated transfection, or electroporation (Davis, L., Dibner, M. , Battey, I., Basic Methods in Molecular Biology, 1986)).

The constructs in host cells can be used in a conventional manner to produce the gene product encoded by the recombinant sequence. Alternatively, the polypeptides of the invention can be synthetically produced by conventional peptide synthesizers.

Mature proteins can be expressed in mammalian cells, yeast, bacteria, or other cells under the control of appropriate promoters. Cell-free translation systems can also be employed to produce such proteins using RNAs derived from the DNA constructs of the present invention. Appropriate cloning and expression vectors for use with prokaryotic and eukaryotic hosts are described by Sambrook. et al., Molecular Cloning: A Laboratory Manual, Second Edition, (Cold Spring Harbor, New York, 1989), the disclosure of which is hereby incorporated by reference.

Transcription of a DNA encoding the polypeptides of the present invention by higher eukaryotes is increased by inserting an enhancer sequence into the vector. Enhancers are cis-acting elements of DNA, usually about from 10 to 300 bp, that act on a promoter to increase its transcription. Examples include the SV40 enhancer on the late side of the replication origin (bp 100 to 270), a cytomegalovirus early promoter enhancer, a polyoma enhancer on the late side of the replication origin, and adenovirus enhancers.

DESCRIPTION OF FIGURES:

Generally, recombinant expression vectors will include origins of replication and selectable markers permitting transformation of the host cell, e.g., the ampicillin resistance gene of E. coli and S. cerevisiae TRP1 gene, and a promoter derived from a highly-expressed gene to direct transcription of a downstream structural sequence. Such promoters can be derived from operons encoding glycolytic enzymes such as 3-phosphoglycerate kinase (PGK), *-factor, acid phosphatase, or **heat shock proteins**, among others. The heterologous structural sequence is assembled in appropriate phase with translation initiation and termination sequences, and preferably, a leader sequence capable of directing secretion of translated protein into the periplasmic space or extracellular medium. Optionally, the heterologous sequence can encode a fusion protein including an N-terminal identification peptide imparting desired characteristics, e.g., stabilization or simplified purification of expressed recombinant product.

Useful expression vectors for bacterial use are constructed by inserting a structural DNA sequence encoding a desired protein together with suitable translation initiation and termination signals in operable reading phase with a functional promoter. The vector will comprise one or more phenotypic selectable markers and an origin of replication to ensure maintenance of the vector and to, if desirable, provide amplification within the host. Suitable prokaryotic hosts for transformation include E. coli, Bacillus subtilis, Salmonella typhimurium and various species within the genera Pseudomonas, Streptomyces,.and Staphylococcus, although others may also be employed as a matter of choice.

As a representative but nonlimiting example, useful expression vectors for bacterial use can comprise a selectable marker and bacterial origin of replication derived from commercially available plasmids comprising genetic elements of the well known cloning vector pBR322 (ATCC 37017). Such commercial vectors include, for example, pKK223-3 (Pharmacia Fine Chemicals, Uppsala, Sweden) and GEM1 (Promega Biotec, Madison, Wis., USA). These pBR322 "backbone" sections are combined with an appropriate promoter and the structural sequence to be expressed.

Following transformation of a suitable host strain and growth of the host strain to an appropriate cell density, the selected promoter is derepressed by appropriate means (e.g., temperature shift or chemical induction) and cells are cultured for an additional period.

Cells are typically harvested by centrifugation, disrupted by physical or chemical means, and the resulting crude extract retained for further purification.

Microbial cells employed in expression of proteins can be disrupted by any convenient method, including freeze-thaw cycling, sonication, mechanical disruption, or use of cell lysing agents.

Various mammalian cell culture systems can also be employed to express recombinant protein. Examples of mammalian expression systems include the COS-7 lines of monkey kidney fibroblasts, described by Gluzman, Cell, 23:175 (1981), and other cell lines capable of expressing a compatible vector, for example, the C127, 3T3, CHO, HeLa and BHK cell lines. Mammalian expression vectors will comprise an origin of replication, a suitable promoter and enhancer, and also any necessary ribosome binding sites, polyadenylation site, splice donor and acceptor sites, transcriptional termination sequences, and 5' flanking nontranscribed sequences. DNA sequences derived from the SV40 viral genome, for example, SV40 origin, early promoter, enhancer, splice, and polyadenylation sites may be used to provide the required nontranscribed genetic elements.

VEGF2 is recovered and purified from recombinant cell cultures by methods used heretofore, including ammonium sulfate or ethanol precipitation, acid extraction, anion or cation exchange chromatography, phosphocellulose chromatography, hydrophobic interaction chromatography, affinity chromatography, hydroxyapatite chromatography and lectin chromatography. It is preferred to have low concentrations (approximately 0.1-5mM) of calcium ion present during purification (Price, et al., J. Biol. Chem., 244:917 (1969)). Protein refolding steps can be used, as necessary, in completing configuration of the mature protein. Finally, high performance liquid chromatography (HPLC) can be employed for final purification steps.

The polypeptides of the present invention may be a naturally purified product, or a product of chemical synthetic procedures, or produced by recombinant techniques from a prokaryotic or eukaryotic host (for example, by bacterial, yeast, higher plant, insect and mammalian cells in culture). Depending upon the host employed in a recombinant production procedure, the polypeptides of the present invention may be glycosylated with mammalian or other eukaryotic carbohydrates or may be nonglycosylated.

VEGF2 is useful as a wound healing agent, particularly where it is necessary to re-vascularize damaged tissues, or where new capillary angiogenesis is important. Therefore, it may be used for treatment of full-thickness wounds such as dermal ulcers, including pressure sores, venous ulcers, and diabetic ulcers. In addition, it can be used in the treatment of full-thickness burns and injuries where angiogenesis is desired to prepare the burn in injured sites for a skin graft and flap. In this case, it should be applied directly at the sites. Similar, VEGF2 can be used in plastic surgery when reconstruction is required following a burn, other trauma, or even for cosmetic purposes.

VEGF2 may also be used to induce the growth of damaged bone, periodontium or ligament tissue. It I may be used in periodontal **disease** where VEGF2 is applied in a methylcellulose gel to the roots of the **diseased** teeth, the treatment could lead to the formation of new bone and cementum with collagen fiber ingrowths. It can be used for regenerating supporting tissues of teeth, including alveolar bone, cementum and periodontal ligament, that have been damaged by **disease** and trauma.

Since angiogenesis is important in keeping wounds clean and noninfected, VEGF2 may be used in association with surgery and following the repair of cuts. It should be particularly useful in the treatment of abdominal wounds where there is a high risk of infection.

VEGF2 can be used for the promotion of endothelialization in **vascular** graft surgery. In the case of **vascular** grafts using either transplanted or synthetic material, VEGF2 can be applied to the surface of the graft or at the junction to promote the growth of the **vascular** endothelial cells. One derivation of this is that VEGF2 can be used to repair the damage of myocardial infarction and other occasions where coronary bypass surgery is needed by stimulating the growth of the transplanted tissue. Related to this is the use of VEGF2 to repair the cardiac **vascular** system after ischemia.

The identification of VEGF2 can be used for the generation of certain inhibitors of **vascular** endothelial growth factor. Since angiogenesis and neovascularization are essential steps in solid tumor growth, inhibition of angiogenic activity of the **vascular** endothelial growth factor is very useful to prevent the further growth, retard, or even regress solid tumors. Although the level of expression of VEGF2 is extremely low in normal tissues including breast, it can be found expressed at moderate levels in at least two breast tumor cell lines that are derived from malignant tumors. It is, therefore, possible that VEGF2 is involved in tumor angiogenesis and growth. VEGF2 can be used for in vitro culturing of **vascular** endothelial cells, where it can be added to the conditional medium to a concentration from 10 pg/ml to 10 ng/ml.

The polypeptide of the present invention may also be employed in accordance with the present invention by expression of such polypeptide in vivo, which is often referred to as "gene therapy."

Thus, for example, cells such as bone marrow cells may be engineered with a polynucleotide (DNA or RNA) encoding for the polypeptide ex vivo, the engineered cells are then provided to a patient to be treated with the polypeptide. Such methods are well-known in the art. For example, cells may be engineered by procedures known in the art by use of a retroviral particle containing RNA encoding for the polypeptide of the present invention. Similarly, cells may be engineered in vivo for expression of the polypeptide in vivo, for example, by procedures known in the art. As known in the art, a producer cell for producing a retroviral particle containing RNA encoding the polypeptide of the present invention may be **administered** to a patient for engineering cells it vivo and expression of the polypeptide in vivo. These and other methods for **administering** a polypeptide of the present invention by such methods should be apparent to those skilled in the art from the teachings of the present invention. For example, the expression vehicle for engineering cells may be other than a retroviral particle, for example, an adenovirus, which may be used to engineering cells in vivo after combination with a suitable delivery vehicle.

The polypeptide of the present invention may be employed in combination with a suitable pharmaceutical carrier. Such compositions comprise a therapeutically effective amount of the protein, and a pharmaceutically acceptable carrier or excipient. Such a carrier includes but is not limited to saline, buffered saline, dextrose, water, glycerol, ethanol, and combinations thereof. The formulation should suit the mode of administration.

DESCRIPTION OF FIGURES:

The invention also provides a pharmaceutical pack or kit comprising one or more containers filled with one or more of the ingredients of the pharmaceutical compositions of the invention. Associated with such container(s) can be a notice in the form prescribed by a governmental agency regulating the manufacture, use or sale of pharmaceuticals or biological products, which notice reflects approval by the agency of manufacture, use or sale for human administration. In addition, the polypeptide of the present invention may be employed on conjunction with other therapeutic compounds.

The pharmaceutical compositions may be administered in a convenient manner, such as the oral, and intravenous routes, and is preferably administered topically. The amounts and dosage regimens of VEGF2 administered to a subject will depend on a number of factors, such as the mode of administration, the nature of the **condition** being treated, the body weight of the subject being treated and the judgment of the prescribing physician. Generally speaking, it is given, for example, in therapeutically effective doses of at least about 10 mu g/kg body weight and, in most cases, it would be administered in an amount not in excess of about 8 mg/kg body weight per day and preferably the dosage is from about 10 mu g/kg body weight to about 1 mg/kg body weight

daily, taking into the account the routes of administration, symptoms, etc.
The sequences of the present invention are also valuable for chromosome identification. The sequence is specifically targeted to and can hybridize with a particular location on an individual human chromosome. Moreover, there is a current need for identifying particular sites on the chromosome. Few chromosome marking reagents based on actual sequence data (repeat polymorphism's) are presently available for marking chromosomal location. The mapping of DNAs to chromosomes according to the present invention is an important first step in correlating those sequences with genes associated with **disease**.
Briefly, sequences can be mapped to chromosomes by preparing PCR primers (preferably 15-25 bp) from the cDNA. Computer analysis of the cDNA is used to rapidly select primers that do not span more than one exon in the genomic DNA, thus complicating the amplification process. These primers are then used for PCR screening of somatic cell hybrids containing individual human chromosomes. Only those hybrids containing the human gene corresponding to the primer will yield an amplified fragment.
PCR mapping of somatic cell hybrids is a rapid procedure for assigning a particular DNA to a particular chromosome. Using the present invention with the same oligonucleotide primers, sublocalization can be achieved with panels of fragments from specific chromosomes or pools of large genomic clones in an analogous manner. Other mapping strategies that can similarly be used to map to its chromosome include in situ hybridization, prescreening with labeled flow-sorted chromosomes and preselection by hybridization to construct chromosome specificcDNA libraries.
Fluorescence in situ hybridization (FISH) of a cDNA clone to a metaphase chromosomal spread can be used to provide a precise chromosomal location in one step. This technique can be used with cDNA as short as 500 or 600 bases; however, clones larger than 2,000 bp have a higher likelihood of binding to a unique chromosomal location with sufficient signal intensity for simple detection. FISH requires use of the clone from which the EST was derived, and the longer the better. For example, 2,000 bp is good, 4,000 is better, and more than 4,000 is probably not necessary to get good results a reasonable percentage of the time. For a review of this technique, see Verma et al., Human Chromosomes: a Manual of Basic Techniques. Pergamon Press, New York (1988).
Once a sequence has been mapped to a precise chromosomal location, the physical position of the sequence on the chromosome can be correlated with genetic map data. (Such data are found, for example, in V. McKusick, Mendelian Inheritance in Man (available on line through Johns Hopkins University Welch Medical Library). The relationship between genes and **diseases** that have been mapped to the same chromosomal region are then identified through linkage analysis (coinheritance of physically adjacent genes).
Next, it is necessary to determine the differences in the cDNA or genomic sequence between affected and unaffected individuals. If a mutation is observed in some or all of the affected individuals but not in any normal individuals, then the mutation is likely to be the causative agent of the ***disease.***
With current resolution of physical mapping and genetic mapping techniques, a cDNA precisely localized to a chromosomal region associated with the ***disease*** could be one of between 50 and 500 potential causative genes. (This assumes 1 megabase mapping resolution and one gene per 20 kb).
Comparison of affected and unaffected individuals generally involves first looking for structural alterations in the chromosomes, such as deletions or translocations that are visible from chromosome spreads or detectable using PCR based on that cDNA sequence. Ultimately, complete sequencing of genes from several individuals is required to confirm the presence of a mutation and to distinguish mutations from polymorphisms.
The present invention is further directed to inhibiting VEGF2 in vivo by the use of antisense technology. Antisense technology can be used to control gene expression through triple-helix formation or antisense DNA or RNA, both of which methods are based on binding of a polynucleotide to DNA or RNA. For example, the 5' coding portion of the mature polynucleotide sequence, which encodes for the polypeptide of the present invention, is used to design an antisense RNA oligonucleotide of from 10 to 40 base pairs in length. A DNA oligonucleotide is designed to be complementary to a region of the gene involved in transcription (triple helix-see Lee et al, Nucl. Acids Res., 6:3073 (1979); Cooney et al, Science, 241:456 (1988); and Dervan et al, Science, 251:

1360 (1991), thereby preventing transcription and the production of VEGF2. The antisense RNA oligonucleotide hybridizes to the mRNA in vivo and blocks translation of an mRNA molecule into the VEGF2 (antisense-Okano, J. Neurochem., 56:560 (1991); Oligodeoxynucleotides as Antisense Inhibitors of Gene Expression, CRC Press, Boca Raton, Fla. (1988)).

Alternatively, the oligonucleotides described above can be delivered to cells by procedures in the art such that the antisense RNA or DNA may be expressed ill vivo to inhibit production of VEGF2 in the manner described above. Antisense constructs to VEGF2, therefore, may inhibit the angiogenic activity of the VEGF2 and prevent the further growth or even regress solid tumors, since angiogenesis and neovascularization are essential steps in solid tumor growth. These antisense constructs may also be used to treat rheumatoid arthritis, psoriasis and diabetic retinopathy which are all characterized by abnormal angiogenesis.

The polypeptides, their fragments or other derivatives, or analogs thereof, or cells expressing them can be used as an immunogen to produce antibodies thereto. These antibodies can be, for example, polyclonal or monoclonal antibodies. The present invention also includes chimeric, single chain, and humanized antibodies, as well as Fab fragments, or the product of an Fab expression library. Various procedures known in the art may be used for the production of such antibodies and fragments.

Antibodies generated against the polypeptide corresponding to a sequence of the present invention can be obtained by direct injection of the polypeptide into an animal or by administering the polypeptide to an animal, preferably a nonhuman. The antibody so obtained will then bind the polypeptide itself. In this manner, even a sequence encoding only a fragment of the polypeptide can be used to generate antibodies binding the whole native polypeptide. Such antibodies can then be used to isolate the polypeptide from tissue expressing that polypeptide.

For preparation of monoclonal antibodies, any technique which provides antibodies produced by continuous cell line cultures can be used. Examples include the hybridoma technique (Kohler and Milstein, 1975, Nature, 256:495-497), the trioma technique, the human B-cell hybridoma technique (Kozbor et al., 1983, Immunology Today 4:72), and the EBV-hybridoma technique to produce human monoclonal antibodies (Cole, et al., 1985, in Monoclonal Antibodies and Cancer Therapy, Alan R. Liss, Inc., pp. 77-96).

Techniques described for the production of single chain antibodies (U.S. Pat. No. 4,946,778) can be adapted to produce single chain antibodies to immunogenic polypeptide products of this invention.

Neutralization antibodies can be identified and applied to mask the ***vascular*** endothelial growth factor, and that has been shown in mice model systems against VEGF. VEGF2 can also be inactivated by certain dominant negative mutants within the gene itself. It is known that both PDGF alpha and beta form either heterodimers or homodimers, and VEGF forms homodimers. Similar interaction between VEGF2 could be expected. These antibodies therefore may be used to block the angiogenic activity of VEGF2 and retard the growth of solid tumors. These antibodies may also be used to treat inflammation caused by the increased **vascular** permeability which results from the presence of VEGF2.

These antibodies may further be used in an immunoassay to detect the presence of tumors in certain individuals. Enzyme immunoassay can be performed from the blood sample of an individual. Elevated levels of of VEGF2 can be considered diagnostic of cancer.

DESCRIPTION OF FIGURES:

The present invention is also directed to antagonist/inhibitors of the polypeptides of the present invention. The antagonist/ inhibitors are those which inhibit or eliminate the function of the polypeptide.

Thus, for example, antagonists bind to a polypeptide of the present invention and inhibit or eliminate its function. The antagonist, for example, could be an antibody against the polypeptide which binds to the polypeptide or, in some cases, an oligonucleotide. An example of an inhibitor is a small molecule which binds to and occupies the catalytic site of the polypeptide thereby making the catalytic site inaccessible to substrate such that normal biological activity is prevented. Examples of small molecules include but are not limited to small peptides or peptide-like molecules.

Truncated versions of VEGF2 can also be produced that are capable of

interacting with wild type VEGF2 form dimers that fail activate endothelial cell growth, therefore inactivated the endogenous VEGF2. Or, mutant forms of VEGF2 form dimers themselves and occupies the ligand binding domain of the proper tyrosine Kinase receptors on the target cell surface, but fail to activate the cell growth.

Alternatively, antagonists to the polypeptides of the present invention may be employed which bind to the receptors to which a polypeptide of the present invention normally binds. The antagonists may be closely related proteins such that they recognize and bind to the receptor sites of the natural protein, however, they are inactive forms of the natural protein and thereby prevent the action of VEGF2 since receptor sites are occupied. In these ways, the action of the VEGF2 is prevented and the antagonist/inhibitors may be used therapeutically as an anti-tumor drug by occupying the receptor sites of tumors which are recognized by VEGF2 or by inactivating VEGF2 itself. The antagonist/inhibitors may also be used to prevent inflammation due to the increased **vascular** permeability action of VEGF2. The antagonist/inhibitors may also be used to treat solid tumor growth, diabetic retinopathy, psoriasis and rheumatoid arthritis.

The antagonist/inhibitors may be employed in a composition with a pharmaceutically acceptable carrier, e.g., as hereinabove described.

The present invention will be further described with reference to the following examples; however, it is to be understood that the present invention is not limited to such examples. All parts or amounts, unless otherwise specified, are by weight.

In order to facilitate understanding of the following examples, certain frequently occurring methods and/or terms will be described.

"Plasmids" are designated by a lower case p preceded and/or followed by capital letters and/or numbers. The starting plasmids herein are either commercially available, publicly available on an unrestricted basis, or can be constructed from available plasmids in accord with published procedures. In addition, equivalent plasmids to those described are known in the art and will be apparent to the ordinarily skilled artisan.

"Digestion" of DNA refers to catalytic cleavage of the DNA with a restriction enzyme that acts only at certain sequences in the DNA. The various restriction enzymes used herein are commercially available and their reaction ***conditions*** , cofactors and other requirements were used as would be known to the ordinarily skilled artisan. For analytical purposes, typically 1 mu g of plasmid or DNA fragment is used with about 2 units of enzyme in about 20 mu l of buffer solution. For the purpose of isolating DNA fragments for plasmid construction, typically 5 to 50 mu g of DNA are digested with 20 to 250 units of enzyme in a larger volume. Appropriate buffers and substrate amounts for particular restriction enzymes are specified by the manufacturer. Incubation times of about 1 hour at 37 degrees C. are ordinarily used, but may vary in accordance with the supplier's instructions. After digestion the reaction is electrophoresed directly on a poly-acrylamide gel to isolate the desired fragment.

Size separation of the cleaved fragments is performed using 8 percent polyacrylamide gel described by Goeddel, D. et al., Nucleic Acids Res., 8:4057 (1980).

"Oligonucleotides" refers to either a single stranded polydeoxynucleotide or two complementary polydeoxynucleotide strands which may be chemically synthesized. Such synthetic oligonucleotides have no 5' phosphate and thus will not ligate to another oligonucleotide without adding a phosphate with an ATP in the presence of a kinase. A synthetic oligonucleotide will ligate to a fragment that has not been dephosphorylated.

"Ligation" refers to the process of forming phosphodiester bonds between two double stranded nucleic acid fragments (Maniatis, T. , et al., Id., p. 146). Unless otherwise provided, ligation may be accomplished using known buffers and ***conditions*** with 10 units of T4 DNA ligase ("ligase") per 0.5 mu g of approximately equimolar amounts of the DNA fragments to be ligated.

Unless otherwise stated, transformation was performed as described by the method of Graham, F. and Van der Eb, A., Virology, 52:456-457 (1973). !

AB Disclosed is a human VEGF2 polypeptide and DNA(RNA) encoding such VEGF2 polypeptides. Also provided is a procedure for producing such polypeptide by recombinant techniques and antibodies and antagonist against such polypeptide. Such polypeptides may be combined with a suitable

pharmaceutical carrier or diluent to provide diagnostic, therapeutic and/or prophylactic effects against various diseases. Also provided are methods of using the antibodies and antagonists to inhibit the action of VEGF2 for therapeutic purposes.

CLMN 20 89 Figure(s).

FIGS. 1A-D (FIG. 1A shows the first portions of the polynucleotide sequence encoding VEGF2 and the amino acid sequence for VEGF2, and FIGS. 1B, 1C and 1D, respectively continue with the sequential portions of each sequence began in FIG. 1A) collectively depict the polynucleotide sequence (SEQ ID NO:1) which encodes VEGF2, and the corresponding amino acid sequence (SEQ ID NO:2) for the VEGF2 polypeptide comprising 350 amino acid residues of which approximately the first 24 amino acids represent the leader sequence. The standard one-letter codes are utilized to depict the amino acid residues encoded by the polynucleotide triplets.

FIGS. 2A-B collectively depict polypeptide sequences in alignment and show the alignment of VEGF2 with the other growth factor PDGF alpha, PDGF beta, and VEGF. FIG. 2A depicts Nterminal portions of the polypeptide sequences and FIG. 2A continues with C-terminal portions of the polypeptide sequences. The four lines in each comparative row depict, respectively, the PDGF alpha polypeptide sequence (SEQ ID NO:7), the PDGF beta polypeptide sequence (SEQ ID NO:8), the VEGF polypeptide sequence (SEQ ID NO:9) and the VEGF2 polypeptide sequence. The amino acid residues are illustrated in FIGS. 2A and 2B by the standard one-letter codes.

FIG. 3 shows, in table-form, the percent homology between PDGF alpha, PDGF beta, VEGF and VEGF2.

FIG. 4 shows the presence of mRNA for VEGF2 in breast tumor cell lines.

FIG. 5 depicts the results of a Northern blot analysis of VEGF2 in human adult tissues.

FIG. 6 shows the results of running VEGF2 and SDS-PAGE gel after in vitro transcription/translation. The full length and partial VEGF2 cDNA were transcribed and translated in a coupled reaction in the presence of 35S-methionine. The translated products were analyzed by 4-20% gradient SDS PAGE and exposed to X-ray film.

In accordance with one aspect of the present invention, there is provided an isolated nucleic acid (polynucleotide) which encodes for the mature polypeptide having the deduced amino acid sequence of SEQ ID NO:2 or for the mature polypeptide encoded by the cDNA of the clone deposited as ATCC Deposit No. 75698, on Mar. 4, 1994, with ATCC, 10801 University Boulevard, Manassas, Va. 20110-2209. Since the strain referred to is being maintained under the terms of the Budapest Treaty, it will be made available to a patent office signatory to the Budapest Treaty. If a patent should issue which is directed to the present invention, upon the issuance of such a patent the deposited strain of ATCC 75698 will be irrevocably and without restriction released to the public, excepting for those restrictions permitted by enforcement of the patent.

A polynucleotide encoding a polypeptide of the present invention may be obtained from early stage human embryo (week 8 to 9) osteoclastomas, adult heart or several breast cancer cell lines. The polynucleotide of this invention was discovered in a cDNA library derived from early stage human embryo week 9. It is structurally related to the VEGF/PDGF family. It contains an open reading frame encoding a protein of about 350 amino acid residues of which approximately the first 24 amino acid residues are likely to be leader sequence such that the mature protein comprises 326 amino acids, and which protein exhibits the highest homology to **vascular** endothelial growth factor (30% identity), followed by PDGF alpha (23%) and PDGF beta (22%), (see FIG. 3). It is particularly important that all eight cysteines are conserved within all four members of the family (see boxed areas of FIG. 2). In addition, the signature for the PDGF/VEGF family, PXCVXXXRCXGCCN, (SEQ ID NO:3) is conserved in VEGF2 (see FIG. 2). The homology between VEGF2, VEGF and the two PDGFs is at the protein sequence level. No nucleotide sequence homology can be detected, and therefore, it would be difficult to isolate the VEGF2 through simple approaches such as low stringency hybridization.

The polynucleotide of the present invention may be in the form of RNA or in the form of DNA, which DNA includes cDNA, genomic DNA, and synthetic DNA. The DNA may be double-stranded or single-stranded, and if single

stranded may be the coding strand or non-coding (anti-sense) strand. The coding sequence which encodes the mature polypeptide may be identical to the coding sequence shown in SEQ ID NO:1 or that of the deposited clone or may be a different coding sequence which coding sequence, as a result of the redundancy or degeneracy of the genetic code, encodes the same, mature polypeptide as the DNA of SEQ ID NO:1 or the deposited cDNA.

The polynucleotide which encodes for the mature polypeptide of FIG. 1 or for the mature polypeptide encoded by the deposited cDNA may include: only the coding sequence for the mature polypeptide; the coding sequence for the mature polypeptide and additional coding sequence such as a leader or secretory sequence or a proprotein sequence; the coding sequence for the mature polypeptide (and optionally additional coding sequence) and non-coding sequence, such as introns or non-coding sequence 5' and/or 3' of the coding sequence for the mature polypeptide.

Thus, the term "polynucleotide encoding a polypeptide" encompasses a polynucleotide which includes only coding sequence for the polypeptide as well as a polynucleotide which includes additional coding and/or non-coding sequence.

The present invention further relates to variants of the hereinabove described polynucleotides which encode for fragments, analogs and derivatives of the polypeptide having the deduced amino acid sequence of FIG. 1 or the polypeptide encoded by the cDNA of the deposited clone. The variant of the polynucleotide may be a naturally occurring allelic variant of the polynucleotide or a non-naturally occurring variant of the polynucleotide.

Thus, the present invention includes polynucleotides encoding the same mature polypeptide as shown in FIG. 1 or the same mature polypeptide encoded by the cDNA of the deposited clone as well as variants of such polynucleotides which variants encode for an fragment, derivative or analog of the polypeptide of FIG. 1 or the polypeptide encoded by the cDNA of the deposited clone. Such nucleotide variants include deletion variants, substitution variants and addition or insertion variants.

As hereinabove indicated, the polynucleotide may have a coding sequence which is a naturally occurring allelic variant of the coding sequence shown in SEQ ID NO:1 or of the coding sequence of the deposited clone. As known in the art, an allelic variant is an alternate form of a polynucleotide sequence which have a substitution, deletion or addition of one or more nucleotides, which does not substantially alter the function of the encoded polypeptide.

The present invention also includes polynucleotides, wherein the coding sequence for the mature polypeptide may be fused in the same reading frame to a polynucleotide which aids in expression and secretion of a polypeptide from a host cell, for example, a leader sequence which functions as a secretory sequence for controlling transport of a polypeptide from the cell. The polypeptide having a leader sequence is a preprotein and may have the leader sequence cleaved by the host cell to form the mature form of the polypeptide. The polynucleotides may also encode for a proprotein which is the mature protein plus additional 5' amino acid residues. A mature protein having a prosequence is a proprotein and is an inactive form of the protein. Once the prosequence is cleaved an active mature protein remains.

Thus, for example, the polynucleotide of the present invention may encode for a mature protein, or for a protein having a prosequence or for a protein having both a prosequence and presequence (leader sequence).

The polynucleotides of the present invention may also have the coding sequence fused in frame to a marker sequence which allows for purification of the polypeptide of the present invention. The marker sequence may be a hexa-histidine tag supplied by a pQE-9 vector to provide for purification of the mature polypeptide fused to the marker in the case of a bacterial host, or, for example, the marker sequence may be a hemagglutinin (HA) tag when a mammalian host, e.g. COS-7 cells, is used. The HA tag corresponds to an epitope derived from the influenza hemagglutinin protein (Wilson, I., et al., Cell, 37:767 (1984)).

The present invention further relates to polynucleotides which hybridize to the hereinabove-described sequences if there is at least 50% and preferably 70% identity between the sequences. The present invention

particularly relates to polynucleotides which hybridize under stringent **conditions** to the hereinabovedescribed polynucleotides . As herein used, the term "stringent **conditions**" means hybridization will occur only if there is at least 95% and preferably at least 97% identity between the sequences. The polynucleotides which hybridize to the hereinabove described polynucleotides in a preferred embodiment encode polypeptides which retain substantially the same biological function or activity as the mature polypeptide encoded by the cDNA of SEQ ID NO:2 or the deposited cDNA.

The deposit(s) referred to herein will be maintained under the Budapest Treaty on the International Recognition of the Deposit of Microorganisms for the purposes of Patent Procedure. These deposits are provided merely as a convenience and are not an admission that a deposit is required under 35 U.S.C. section 112. The sequence of the polynucleotides contained in the deposited materials, as well as the amino acid sequence of the polypeptides encoded thereby, are incorporated herein by reference and are controlling in the event of any conflict with the description of sequences herein. A license may be required to make, use or sell the deposited materials, and no such license is hereby granted.

The present invention further relates to a VEGF2 polypeptide which has the deduced amino acid sequence of SEQ ID NO:2 or which has the amino acid sequence encoded by the deposited cDNA, as well as fragments, analogs and derivatives of such polypeptide.

The terms "fragment," "derivative" and "analog" when referring to the polypeptide of SEQ ID NO:2 or that encoded by the deposited cDNA, means a polypeptide which retains essentially the same biological function or activity as such polypeptide. Thus, an analog includes a proprotein which can be activated by cleavage of the proprotein portion to produce an active mature polypeptide.

The polypeptide of the present invention may be a recombinant polypeptide, a natural polypeptide or a synthetic polypeptide, preferably a recombinant polypeptide.

The fragment, derivative or analog of the polypeptide of SEQ ID NO:2 or that encoded by the deposited cDNA may be (i) one in which one or more of the amino acid residues are substituted with a conserved or non-conserved amino acid residue (preferably a conserved amino acid residue) and such substituted amino acid residue may or may not be one encoded by the genetic code, or (ii) one in which one or more of the amino acid residues includes a substituent group, or (iii) one in which the mature polypeptide is fused with another compound, such as a compound to increase the half-life of the polypeptide (for example, polyethylene glycol), or (iv) one in which the additional amino acids are fused to the mature polypeptide, such as a leader or secretory sequence or a sequence which is employed for purification of the mature polypeptide or a proprotein sequence. Such fragments, derivatives and analogs are deemed to be within the scope of those skilled in the art from the teachings herein.

The polypeptides and polynucleotides of the present invention are preferably provided in an isolated form, and preferably are purified to homogeneity.

The term "isolated" means that the material is removed from its original environment (e.g., the natural environment if it is naturally occurring). For example, a naturally-occurring polynucleotide or polypeptide present in a living animal is not isolated, but the same polynucleotide or DNA or polypeptide, separated from some or all of the coexisting materials in the natural system, is isolated. Such polynucleotide could be part of a vector and/or such polynucleotide or polypeptide could be part of a composition, and still be isolated in that such vector or composition is not part of its natural environment.

The present invention also relates to vectors which include polynucleotides of the present invention, host cells which are genetically engineered with vectors of the invention and the production of polypeptides of the invention by recombinant techniques.

Host cells are genetically engineered (transduced or transformed or transfected) with the vectors of this invention which may be, for example, a cloning vector or an expression vector. The vector may be, for

example, in the form of a plasmid, a viral particle, a phage, etc. The engineered host cells can be cultured in conventional nutrient media modified as appropriate for activating promoters, selecting transformants or amplifying the VEGF2 genes. The culture conditions, such as temperature, pH and the like, are those previously used with the host cell selected for expression, and will be apparent to the ordinarily skilled artisan.

The polynucleotide of the present invention may be employed for producing a polypeptide by recombinant techniques. Thus, for example, the polynucleotide sequence may be included in any one of a variety of expression vehicles, in particular vectors or plasmids for expressing a polypeptide. Such vectors include chromosomal, nonchromosomal and synthetic DNA sequences, e.g., derivatives of SV40; bacterial plasmids; phage DNA; yeast plasmids; vectors derived from combinations of plasmids and phage DNA, viral DNA such as vaccinia, adenovirus, fowl pox virus, and pseudorabies. However, any other plasmid or vector may be used as long as it is replicable and viable in the host.

As hereinabove described, the appropriate DNA sequence may be inserted into the vector by a variety of procedures. In general, the DNA sequence is inserted into an appropriate restriction endonuclease sites by procedures known in the art. Such procedures and others are deemed to be within the scope of those skilled in the art.

The DNA sequence in the expression vector is operatively linked to an appropriate expression control sequence(s) (promoter) to direct mRNA synthesis. As representative examples of such promoters, there may be mentioned: LTR or SV40 promoter, the E. coli. lac or trp, the phage lambda PL promoter and other promoters known to control expression of genes in prokaryotic or eukaryotic cells or their viruses. The expression vector also contains a ribosome binding site for translation initiation and a transcription terminator. The vector may also include appropriate sequences for amplifying expression.

In addition, the expression vectors preferably contain a gene to provide a phenotypic trait for selection of transformed host cells such as dihydrofolate reductase or neomycin resistance for eukaryotic cell culture, or such as tetracycline or ampicillin resistance in E. coli.

The vector containing the appropriate DNA sequence as herein above described, as well as an appropriate promoter or control sequence, may be employed to transform an appropriate host to permit the host to express the protein. As representative examples of appropriate hosts, there may be mentioned: bacterial cells, such as E. coli, Salmonella typhimurium Streptomyces; fungal cells, such as yeast; insect cells, such as Drosophila and Sf9; animal cells such as CHO, COS or Bowes melanoma; plant cells, etc. The selection of an appropriate host is deemed to be within the scope of those skilled in the art from the teachings herein.

More particularly, the present invention also includes recombinant constructs comprising one or more of the sequences as broadly described above. The constructs comprise a vector, such as a plasmid or viral vector, into which a sequence of the invention has been inserted, in a forward or reverse orientation. In a preferred aspect of this embodiment, the construct further comprises regulatory sequences, including, for example, a promoter, operably linked to the sequence. Large numbers of suitable vectors and promoters are known to those of skill in the art, and are commercially available. The following vectors are provided by way of example. Bacterial: pQE70, pQE-9 (Qiagen), pBs, phagescript, PsiX174, pBluescript SK, pBsKS, pNH8a, pNH16a, pNH18a, pNH46a (Stratagene); pTrc99A, pKK223-3, pKK233-3, pDR540, PRIT5 (Pharmacia). Eukaryotic: pWLneo, pSV2cat, pOG44, pXT1, pSG (Stratagene) pSVK3, pBPV, pMSG, pSVL (Pharmacia). However, any other plasmid or vector may be used as long as they are replicable and viable in the host.

Promoter regions can be selected from any desired gene using CAT (chloramphenicol transferase) vectors or other vectors with selectable markers. Two appropriate vectors are pKK232-8 and pCM7. Particular named bacterial promoters include lacI, lacZ, T3, T7, gpt, lambda PR, PL and trp. Eukaryotic promoters include CMV immediate early, HSV thymidine kinase, early and late SV40, LTRs from retrovirus, and mouse metallothionein-I. Selection of the appropriate vector and promoter is

well within the level of ordinary skill in the art.

In a further embodiment, the present invention relates to host cells containing the above-described construct. The host cell can be a higher eukaryotic cell, such as a mammalian cell, or a lower eukaryotic cell, such as a yeast cell, or the host cell can be a prokaryotic cell, such as a bacterial cell. Introduction of the construct into the host cell can be effected by calcium phosphate transfection, DEAE-Dextran mediated transfection, or electroporation (Davis, L., Dibner, M. , Battey, I., Basic Methods in Molecular Biology, 1986)).

The constructs in host cells can be used in a conventional manner to produce the gene product encoded by the recombinant sequence. Alternatively, the polypeptides of the invention can be synthetically produced by conventional peptide synthesizers.

Mature proteins can be expressed in mammalian cells, yeast, bacteria, or other cells under the control of appropriate promoters. Cell-free translation systems can also be employed to produce such proteins using RNAs derived from the DNA constructs of the present invention. Appropriate cloning and expression vectors for use with prokaryotic and eukaryotic hosts are described by Sambrook. et al., Molecular Cloning: A Laboratory Manual, Second Edition, (Cold Spring Harbor, New York, 1989), the disclosure of which is hereby incorporated by reference.

Transcription of a DNA encoding the polypeptides of the present invention by higher eukaryotes is increased by inserting an enhancer sequence into the vector. Enhancers are cis-acting elements of DNA, usually about from 10 to 300 bp, that act on a promoter to increase its transcription. Examples include the SV40 enhancer on the late side of the replication origin (bp 100 to 270), a cytomegalovirus early promoter enhancer, a polyoma enhancer on the late side of the replication origin, and adenovirus enhancers.

Generally, recombinant expression vectors will include origins of replication and selectable markers permitting transformation of the host cell, e.g., the ampicillin resistance gene of E. coli and S. cerevisiae TRP1 gene, and a promoter derived from a highly-expressed gene to direct transcription of a downstream structural sequence. Such promoters can be derived from operons encoding glycolytic enzymes such as 3-phosphoglycerate kinase (PGK), *-factor, acid phosphatase, or **heat shock proteins**, among others. The heterologous structural sequence is assembled in appropriate phase with translation initiation and termination sequences, and preferably, a leader sequence capable of directing secretion of translated protein into the periplasmic space or extracellular medium. Optionally, the heterologous sequence can encode a fusion protein including an N-terminal identification peptide imparting desired characteristics, e.g., stabilization or simplified purification of expressed recombinant product.

Useful expression vectors for bacterial use are constructed by inserting a structural DNA sequence encoding a desired protein together with suitable translation initiation and termination signals in operable reading phase with a functional promoter. The vector will comprise one or more phenotypic selectable markers and an origin of replication to ensure maintenance of the vector and to, if desirable, provide amplification within the host. Suitable prokaryotic hosts for transformation include E. coli, Bacillus subtilis, Salmonella typhimurium and various species within the genera Pseudomonas, Streptomyces,.and Staphylococcus, although others may also be employed as a matter of choice.

As a representative but nonlimiting example, useful expression vectors for bacterial use can comprise a selectable marker and bacterial origin of replication derived from commercially available plasmids comprising genetic elements of the well known cloning vector pBR322 (ATCC 37017). Such commercial vectors include, for example, pKK223-3 (Pharmacia Fine Chemicals, Uppsala, Sweden) and GEM1 (Promega Biotec, Madison, Wis., USA). These pBR322 "backbone" sections are combined with an appropriate promoter and the structural sequence to be expressed.

Following transformation of a suitable host strain and growth of the host strain to an appropriate cell density, the selected promoter is derepressed by appropriate means (e.g., temperature shift or chemical

induction) and cells are cultured for an additional period.
Cells are typically harvested by centrifugation, disrupted by physical or chemical means, and the resulting crude extract retained for further purification.
Microbial cells employed in expression of proteins can be disrupted by any convenient method, including freeze-thaw cycling, sonication, mechanical disruption, or use of cell lysing agents.
Various mammalian cell culture systems can also be employed to express recombinant protein. Examples of mammalian expression systems include the COS-7 lines of monkey kidney fibroblasts, described by Gluzman, Cell, 23:175 (1981), and other cell lines capable of expressing a compatible vector, for example, the C127, 3T3, CHO, HeLa and BHK cell lines. Mammalian expression vectors will comprise an origin of replication, a suitable promoter and enhancer, and also any necessary ribosome binding sites, polyadenylation site, splice donor and acceptor sites, transcriptional termination sequences, and 5' flanking nontranscribed sequences. DNA sequences derived from the SV40 viral genome, for example, SV40 origin, early promoter, enhancer, splice, and polyadenylation sites may be used to provide the required nontranscribed genetic elements.
VEGF2 is recovered and purified from recombinant cell cultures by methods used heretofore, including ammonium sulfate or ethanol precipitation, acid extraction, anion or cation exchange chromatography, phosphocellulose chromatography, hydrophobic interaction chromatography, affinity chromatography, hydroxyapatite chromatography and lectin chromatography. It is preferred to have low concentrations (approximately 0.1-5mM) of calcium ion present during purification (Price, et al., J. Biol. Chem., 244:917 (1969)). Protein refolding steps can be used, as necessary, in completing configuration of the mature protein. Finally, high performance liquid chromatography (HPLC) can be employed for final purification steps.
The polypeptides of the present invention may be a naturally purified product, or a product of chemical synthetic procedures, or produced by recombinant techniques from a prokaryotic or eukaryotic host (for example, by bacterial, yeast, higher plant, insect and mammalian cells in culture). Depending upon the host employed in a recombinant production procedure, the polypeptides of the present invention may be glycosylated with mammalian or other eukaryotic carbohydrates or may be nonglycosylated.
VEGF2 is useful as a wound healing agent, particularly where it is necessary to re-vascularize damaged tissues, or where new capillary angiogenesis is important. Therefore, it may be used for treatment of full-thickness wounds such as dermal ulcers, including pressure sores, venous ulcers, and diabetic ulcers. In addition, it can be used in the treatment of full-thickness burns and injuries where angiogenesis is desired to prepare the burn in injured sites for a skin graft and flap. In this case, it should be applied directly at the sites. Similar, VEGF2 can be used in plastic surgery when reconstruction is required following a burn, other trauma, or even for cosmetic purposes.
VEGF2 may also be used to induce the growth of damaged bone, periodontium or ligament tissue. It I may be used in periodontal **disease** where VEGF2 is applied in a methylcellulose gel to the roots of the **diseased** teeth, the treatment could lead to the formation of new bone and cementum with collagen fiber ingrowths. It can be used for regenerating supporting tissues of teeth, including alveolar bone, cementum and periodontal ligament, that have been damaged by **disease** and trauma.
Since angiogenesis is important in keeping wounds clean and noninfected, VEGF2 may be used in association with surgery and following the repair of cuts. It should be particularly useful in the treatment of abdominal wounds where there is a high risk of infection.
VEGF2 can be used for the promotion of endothelialization in **vascular** graft surgery. In the case of **vascular** grafts using either transplanted or synthetic material, VEGF2 can be applied to the surface of the graft or at the junction to promote the growth of the **vascular** endothelial cells. One derivation of this is that VEGF2 can be used to repair the damage of myocardial infarction and other

occasions where coronary bypass surgery is needed by stimulating the growth of the transplanted tissue. Related to this is the use of VEGF2 to repair the cardiac **vascular** system after ischemia.

The identification of VEGF2 can be used for the generation of certain inhibitors of **vascular** endothelial growth factor. Since angiogenesis and neovascularization are essential steps in solid tumor growth, inhibition of angiogenic activity of the **vascular** endothelial growth factor is very useful to prevent the further growth, retard, or even regress solid tumors. Although the level of expression of VEGF2 is extremely low in normal tissues including breast, it can be found expressed at moderate levels in at least two breast tumor cell lines that are derived from malignant tumors. It is, therefore, possible that VEGF2 is involved in tumor angiogenesis and growth.

VEGF2 can be used for in vitro culturing of **vascular** endothelial cells, where it can be added to the conditional medium to a concentration from 10 pg/ml to 10 ng/ml.

The polypeptide of the present invention may also be employed in accordance with the present invention by expression of such polypeptide in vivo, which is often referred to as "gene therapy."

Thus, for example, cells such as bone marrow cells may be engineered with a polynucleotide (DNA or RNA) encoding for the polypeptide ex vivo, the engineered cells are then provided to a patient to be treated with the polypeptide. Such methods are well-known in the art. For example, cells may be engineered by procedures known in the art by use of a retroviral particle containing RNA encoding for the polypeptide of the present invention.

Similarly, cells may be engineered in vivo for expression of the polypeptide in vivo, for example, by procedures known in the art. As known in the art, a producer cell for producing a retroviral particle containing RNA encoding the polypeptide of the present invention may be **administered** to a patient for engineering cells it vivo and expression of the polypeptide in vivo. These and other methods for **administering** a polypeptide of the present invention by such methods should be apparent to those skilled in the art from the teachings of the present invention. For example, the expression vehicle for engineering cells may be other than a retroviral particle, for example, an adenovirus, which may be used to engineering cells in vivo after combination with a suitable delivery vehicle.

The polypeptide of the present invention may be employed in combination with a suitable pharmaceutical carrier. Such compositions comprise a therapeutically effective amount of the protein, and a pharmaceutically acceptable carrier or excipient. Such a carrier includes but is not limited to saline, buffered saline, dextrose, water, glycerol, ethanol, and combinations thereof. The formulation should suit the mode of administration.

The invention also provides a pharmaceutical pack or kit comprising one or more containers filled with one or more of the ingredients of the pharmaceutical compositions of the invention. Associated with such container(s) can be a notice in the form prescribed by a governmental agency regulating the manufacture, use or sale of pharmaceuticals or biological products, which notice reflects approval by the agency of manufacture, use or sale for human administration. In addition, the polypeptide of the present invention may be employed on conjunction with other therapeutic compounds.

The pharmaceutical compositions may be administered in a convenient manner, such as the oral, and intravenous routes, and is preferably administered topically. The amounts and dosage regimens of VEGF2 administered to a subject will depend on a number of factors, such as the mode of administration, the nature of the **condition** being treated, the body weight of the subject being treated and the judgment of the prescribing physician. Generally speaking, it is given, for example, in therapeutically effective doses of at least about 10 mu g/kg body weight and, in most cases, it would be administered in an amount not in excess of about 8 mg/kg body weight per day and preferably the dosage is from about 10 mu g/kg body weight to about 1 mg/kg body weight daily, taking into the account the routes of administration, symptoms, etc.

The sequences of the present invention are also valuable for chromosome identification. The sequence is specifically targeted to and can hybridize with a particular location on an individual human chromosome. Moreover, there is a current need for identifying particular sites on the chromosome. Few chromosome marking reagents based on actual sequence data (repeat polymorphism's) are presently available for marking chromosomal location. The mapping of DNAs to chromosomes according to the present invention is an important first step in correlating those sequences with genes associated with **disease**.

Briefly, sequences can be mapped to chromosomes by preparing PCR primers (preferably 15-25 bp) from the cDNA. Computer analysis of the cDNA is used to rapidly select primers that do not span more than one exon in the genomic DNA, thus complicating the amplification process. These primers are then used for PCR screening of somatic cell hybrids containing individual human chromosomes. Only those hybrids containing the human gene corresponding to the primer will yield an amplified fragment.

PCR mapping of somatic cell hybrids is a rapid procedure for assigning a particular DNA to a particular chromosome. Using the present invention with the same oligonucleotide primers, sublocalization can be achieved with panels of fragments from specific chromosomes or pools of large genomic clones in an analogous manner. Other mapping strategies that can similarly be used to map to its chromosome include in situ hybridization, prescreening with labeled flow-sorted chromosomes and preselection by hybridization to construct chromosome specificcDNA libraries.

Fluorescence in situ hybridization (FISH) of a cDNA clone to a metaphase chromosomal spread can be used to provide a precise chromosomal location in one step. This technique can be used with cDNA as short as 500 or 600 bases; however, clones larger than 2,000 bp have a higher likelihood of binding to a unique chromosomal location with sufficient signal intensity for simple detection. FISH requires use of the clone from which the EST was derived, and the longer the better. For example, 2,000 bp is good, 4,000 is better, and more than 4,000 is probably not necessary to get good results a reasonable percentage of the time. For a review of this technique, see Verma et al., Human Chromosomes: a Manual of Basic Techniques. Pergamon Press, New York (1988).

Once a sequence has been mapped to a precise chromosomal location, the physical position of the sequence on the chromosome can be correlated with genetic map data. (Such data are found, for example, in V. McKusick, Mendelian Inheritance in Man (available on line through Johns Hopkins University Welch Medical Library). The relationship between genes and **diseases** that have been mapped to the same chromosomal region are then identified through linkage analysis (coinheritance of physically adjacent genes).

Next, it is necessary to determine the differences in the cDNA or genomic sequence between affected and unaffected individuals. If a mutation is observed in some or all of the affected individuals but not in any normal individuals, then the mutation is likely to be the causative agent of the **disease**.

With current resolution of physical mapping and genetic mapping techniques, a cDNA precisely localized to a chromosomal region associated with the **disease** could be one of between 50 and 500 potential causative genes. (This assumes 1 megabase mapping resolution and one gene per 20 kb).

Comparison of affected and unaffected individuals generally involves first looking for structural alterations in the chromosomes, such as deletions or translocations that are visible from chromosome spreads or detectable using PCR based on that cDNA sequence. Ultimately, complete sequencing of genes from several individuals is required to confirm the presence of a mutation and to distinguish mutations from polymorphisms.

The present invention is further directed to inhibiting VEGF2 in vivo by the use of antisense technology. Antisense technology can be used to control gene expression through triple-helix formation or antisense DNA or RNA, both of which methods are based on binding of a polynucleotide to DNA or RNA. For example, the 5' coding portion of the mature polynucleotide sequence, which encodes for the polypeptide of the present invention, is used to design an antisense RNA oligonucleotide of from 10

to 40 base pairs in length. A DNA oligonucleotide is designed to be complementary to a region of the gene involved in transcription (triple helix-see Lee et al, Nucl. Acids Res., 6:3073 (1979); Cooney et al, Science, 241:456 (1988); and Dervan et al, Science, 251: 1360 (1991), thereby preventing transcription and the production of VEGF2. The antisense RNA oligonucleotide hybridizes to the mRNA in vivo and blocks translation of an mRNA molecule into the VEGF2 (antisense-Okano, J. Neurochem., 56:560 (1991); Oligodeoxynucleotides as Antisense Inhibitors of Gene Expression, CRC Press, Boca Raton, Fla. (1988)).

Alternatively, the oligonucleotides described above can be delivered to cells by procedures in the art such that the antisense RNA or DNA may be expressed ill vivo to inhibit production of VEGF2 in the manner described above.

Antisense constructs to VEGF2, therefore, may inhibit the angiogenic activity of the VEGF2 and prevent the further growth or even regress solid tumors, since angiogenesis and neovascularization are essential steps in solid tumor growth. These antisense constructs may also be used to treat rheumatoid arthritis, psoriasis and diabetic retinopathy which are all characterized by abnormal angiogenesis.

The polypeptides, their fragments or other derivatives, or analogs thereof, or cells expressing them can be used as an immunogen to produce antibodies thereto. These antibodies can be, for example, polyclonal or monoclonal antibodies. The present invention also includes chimeric, single chain, and humanized antibodies, as well as Fab fragments, or the product of an Fab expression library. Various procedures known in the art may be used for the production of such antibodies and fragments.

Antibodies generated against the polypeptide corresponding to a sequence of the present invention can be obtained by direct injection of the polypeptide into an animal or by administering the polypeptide to an animal, preferably a nonhuman. The antibody so obtained will then bind the polypeptide itself. In this manner, even a sequence encoding only a fragment of the polypeptide can be used to generate antibodies binding the whole native polypeptide. Such antibodies can then be used to isolate the polypeptide from tissue expressing that polypeptide.

For preparation of monoclonal antibodies, any technique which provides antibodies produced by continuous cell line cultures can be used. Examples include the hybridoma technique (Kohler and Milstein, 1975, Nature, 256:495-497), the trioma technique, the human B-cell hybridoma technique (Kozbor et al., 1983, Immunology Today 4:72), and the EBV-hybridoma technique to produce human monoclonal antibodies (Cole, et al., 1985, in Monoclonal Antibodies and Cancer Therapy, Alan R. Liss, Inc., pp. 77-96).

Techniques described for the production of single chain antibodies (U.S. Pat. No. 4,946,778) can be adapted to produce single chain antibodies to immunogenic polypeptide products of this invention.

Neutralization antibodies can be identified and applied to mask the **vascular** endothelial growth factor, and that has been shown in mice model systems against VEGF. VEGF2 can also be inactivated by certain dominant negative mutants within the gene itself. It is known that both PDGF alpha and beta form either heterodimers or homodimers, and VEGF forms homodimers. Similar interaction between VEGF2 could be expected. These antibodies therefore may be used to block the angiogenic activity of VEGF2 and retard the growth of solid tumors. These antibodies may also be used to treat inflammation caused by the increased **vascular** permeability which results from the presence of VEGF2.

These antibodies may further be used in an immunoassay to detect the presence of tumors in certain individuals. Enzyme immunoassay can be performed from the blood sample of an individual. Elevated levels of of VEGF2 can be considered diagnostic of cancer.

The present invention is also directed to antagonist/inhibitors of the polypeptides of the present invention. The antagonist/ inhibitors are those which inhibit or eliminate the function of the polypeptide.

Thus, for example, antagonists bind to a polypeptide of the present invention and inhibit or eliminate its function. The antagonist, for example, could be an antibody against the polypeptide which binds to the polypeptide or, in some cases, an oligonucleotide. An example of an

inhibitor is a small molecule which binds to and occupies the catalytic site of the polypeptide thereby making the catalytic site inaccessible to substrate such that normal biological activity is prevented. Examples of small molecules include but are not limited to small peptides or peptide-like molecules.

Truncated versions of VEGF2 can also be produced that are capable of interacting with wild type VEGF2 form dimers that fail activate endothelial cell growth, therefore inactivated the endogenous VEGF2. Or, mutant forms of VEGF2 form dimers themselves and occupies the ligand binding domain of the proper tyrosine Kinase receptors on the target cell surface, but fail to activate the cell growth.

Alternatively, antagonists to the polypeptides of the present invention may be employed which bind to the receptors to which a polypeptide of the present invention normally binds. The antagonists may be closely related proteins such that they recognize and bind to the receptor sites of the natural protein, however, they are inactive forms of the natural protein and thereby prevent the action of VEGF2 since receptor sites are occupied. In these ways, the action of the VEGF2 is prevented and the antagonist/inhibitors may be used therapeutically as an anti-tumor drug by occupying the receptor sites of tumors which are recognized by VEGF2 or by inactivating VEGF2 itself. The antagonist/inhibitors may also be used to prevent inflammation due to the increased **vascular** permeability action of VEGF2. The antagonist/inhibitors may also be used to treat solid tumor growth, diabetic retinopathy, psoriasis and rheumatoid arthritis.

The antagonist/inhibitors may be employed in a composition with a pharmaceutically acceptable carrier, e.g., as hereinabove described.

The present invention will be further described with reference to the following examples; however, it is to be understood that the present invention is not limited to such examples. All parts or amounts, unless otherwise specified, are by weight.

In order to facilitate understanding of the following examples, certain frequently occurring methods and/or terms will be described.

"Plasmids" are designated by a lower case p preceded and/or followed by capital letters and/or numbers. The starting plasmids herein are either commercially available, publicly available on an unrestricted basis, or can be constructed from available plasmids in accord with published procedures. In addition, equivalent plasmids to those described are known in the art and will be apparent to the ordinarily skilled artisan.

"Digestion" of DNA refers to catalytic cleavage of the DNA with a restriction enzyme that acts only at certain sequences in the DNA. The various restriction enzymes used herein are commercially available and their reaction **conditions**, cofactors and other requirements were used as would be known to the ordinarily skilled artisan. For analytical purposes, typically 1 mu g of plasmid or DNA fragment is used with about 2 units of enzyme in about 20 mu l of buffer solution. For the purpose of isolating DNA fragments for plasmid construction, typically 5 to 50 mu g of DNA are digested with 20 to 250 units of enzyme in a larger volume. Appropriate buffers and substrate amounts for particular restriction enzymes are specified by the manufacturer. Incubation times of about 1 hour at 37 degrees C. are ordinarily used, but may vary in accordance with the supplier's instructions. After digestion the reaction is electrophoresed directly on a poly-acrylamide gel to isolate the desired fragment.

Size separation of the cleaved fragments is performed using 8 percent polyacrylamide gel described by Goeddel, D. et al., Nucleic Acids Res., 8:4057 (1980).

"Oligonucleotides" refers to either a single stranded polydeoxynucleotide or two complementary polydeoxynucleotide strands which may be chemically synthesized. Such synthetic oligonucleotides have no 5' phosphate and thus will not ligate to another oligonucleotide without adding a phosphate with an ATP in the presence of a kinase. A synthetic oligonucleotide will ligate to a fragment that has not been dephosphorylated.

"Ligation" refers to the process of forming phosphodiester bonds between two double stranded nucleic acid fragments (Maniatis, T. , et al., Id.,

p. 146). Unless otherwise provided, ligation may be accomplished using known buffers and **conditions** with 10 units of T4 DNA ligase ("ligase") per 0.5 mu g of approximately equimolar amounts of the DNA fragments to be ligated.
Unless otherwise stated, transformation was performed as described by the method of Graham, F. and Van der Eb, A., Virology, 52:456-457 (1973). !

L69 ANSWER 34 OF 64 USPATFULL on STN
ACCESSION NUMBER: 2002:329451 USPATFULL
TITLE: Adjuvant immune therapy in the treatment of solid tumors through modulation of signaling pathways following engagement of humoral and cell mediated responses
INVENTOR(S): Kindness, George, Middletown, OH, UNITED STATES
Schumm, Brooke, III, Ellicott City, MD, UNITED STATES
Guilford, F. Timothy, Palo Alto, CA, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2002187130	A1	20021212
APPLICATION INFO.:	US 2001-880745	A1	20010613 (9)

RELATED APPLN. INFO.: Continuation-in-part of Ser. No. US 2001-263486, filed on 23 Jan 2001, PENDING
DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: BROOKE SCHUMM, III, DANEKER, MCINTIRE, SCHUMM, PRINCE, GOLDSTEIN, ET A, 210 N CHARLES ST, SUITE 800, BALTIMORE, MD, 21201
NUMBER OF CLAIMS: 70
EXEMPLARY CLAIM: 1
LINE COUNT: 3060
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The invention combines a novel combination with two especially important aspects: first, the invention proposes to simultaneously stimulate response in white blood cells and a patient's tumor cells with a mitogen-challenging compound, preferably a lectin, in the preferred mode the selected lectin being phytohemagglutin ("PHA"), and second, to generate heat shock protein. A method of treatment is set out. The method of manufacturing proposed utilizes a system calculated to better insure sterility and streamline production of the cytokine modulator. A method of testing in conjunction with the therapy is also claimed utilizing clinical assessment of disease activity, patient performance status, and quality of life questionnaire. Should efficacy of a treatment fall off, particularly because of mutation or adaption, the composition and method may be re- applied. The invention is not limited to humans, but is also applicable to mammals. The composition is usable as a stand-alone composition, but preferably is used in conjunction with standard therapy such as radiation, chemotherapy or surgery, particularly surgical therapy, and in conjunction with the administration of cystine, as later defined, to enhance immune system competency.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L69 ANSWER 35 OF 64 USPATFULL on STN
ACCESSION NUMBER: 2002:322035 USPATFULL
TITLE: Composition and method for normalizing impaired or deteriorating neurological function
INVENTOR(S): McCleary, Edward Larry, Golden, CO, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2002182196	A1	20021205
APPLICATION INFO.:	US 2001-837562	A1	20010419 (9)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION

LEGAL REPRESENTATIVE: PATTON BOGGS LLP, ATTORNEYS AT LAW, 2550 M Street, NW, Washington, DC, 20037-1350
NUMBER OF CLAIMS: 52
EXEMPLARY CLAIM: 1
LINE COUNT: 1541
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB A nutritional supplement composition for normalizing impaired or deteriorating neurological function in humans is composed of: at least one agent which promotes synthesis of ATP and/or creatine phosphate in the body, at least one antioxidant for scavenging free radicals in at least one pathway in the body; at least one agent for normalizing or maintaining membrane function and structure in the body; at least one agent for normalizing or maintaining normal neurotransmitter function in the body; at least one agent for down-regulating cortisol action; and at least one agent for suppressing activation of apoptotic pathways in the body. The composition may further contain one or more of: at least one agent for suppressing inflammation in the body; at least one agent for normalizing or maintaining vascular wall function and structure in the body; at least one agent for normalizing or maintaining function of nerve growth factors and/or neurotropic factors in the body; at least one agent for suppressing toxic metal ionic effects; at least one agent for normalizing or maintaining methyl metabolism in the body; at least one agent for normalizing or maintaining metabolism of insulin and glucose in the body; and at least one agent for up-regulating activity of **heat shock proteins** in the body. A method for normalizing impaired neurological function in humans modulating nutrient partitioning in a human involves **administering** the aforementioned composition to the human, preferably on a daily basis, for a therapeutically effective period of time. Preferably, the method further involves having the human follow a stress reduction program, and/or a cognitive retraining program, and/or a dietary program designed to maximize insulin and glucose metabolism.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L69 ANSWER 36 OF 64 USPATFULL on STN
ACCESSION NUMBER: 2002:314377 USPATFULL
TITLE: Endomural therapy
INVENTOR(S): Slepian, Marvin J., Tucson, AZ, UNITED STATES
PATENT ASSIGNEE(S): Endoluminal Therapeutics, Inc. (non-U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2002176849	A1	20021128
APPLICATION INFO.:	US 2002-72766	A1	20020208 (10)

	NUMBER	DATE
PRIORITY INFORMATION:	US 2001-267578P	20010209 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: Patrea L. Pabst, Holland & Knight LLP, One Atlantic Center, Suite 2000, 1201 West Peachtree Street, Atlanta, GA, 30309-3400
NUMBER OF CLAIMS: 33
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 4 Drawing Page(s)
LINE COUNT: 1277
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Methods, devices and materials for the treatment or repair, replacement, transplantation or augmentation of tissues in endomural zones specifically by open surgical, minimally invasive or percutaneous transmural or trans parenchymal application of polymeric material alone or in combination with bioactive agents or cells, have been developed. These methods and systems are useful to repair, alter function, replace function or augment function of the central or endomural aspects of

solid organs or tubular body structures.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L69 ANSWER 37 OF 64 USPATFULL on STN
ACCESSION NUMBER: 2002:287633 USPATFULL
TITLE: Isolated GRP94 ligand binding domain polypeptide and nucleic acid encoding same, and screening methods employing same
INVENTOR(S): Gewirth, Daniel T., Durham, NC, UNITED STATES
Nicchitta, Christopher V., Durham, NC, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2002160496	A1	20021031
APPLICATION INFO.:	US 2001-968436	A1	20011001 (9)

RELATED APPLN. INFO.: Continuation-in-part of Ser. No. WO 2001-US9512, filed on 26 Mar 2001, UNKNOWN

	NUMBER	DATE
PRIORITY INFORMATION:	US 2000-192118P	20000324 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: JENKINS & WILSON, PA, 3100 TOWER BLVD, SUITE 1400, DURHAM, NC, 27707
NUMBER OF CLAIMS: 14
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 17 Drawing Page(s)
LINE COUNT: 5917
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB An isolated GRP94 ligand binding domain polypeptide, an isolated polynucleotide encoding the same, and methods of using the same to identify modulators of Hsp90 proteins.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L69 ANSWER 38 OF 64 USPATFULL on STN
ACCESSION NUMBER: 2002:198588 USPATFULL
TITLE: IDENTIFICATION OF GENE SEQUENCES AND GENE PRODUCTS AND THEIR SPECIFIC FUNCTION AND RELATIONSHIP TO PATHOLOGIES IN A MAMMAL
INVENTOR(S): JENBOUBI, MONCEF, BETHESDA, MD, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2002106688	A1	20020808
APPLICATION INFO.:	US 1997-906487	A1	19970805 (8)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: LYON & LYON LLP, 633 WEST FIFTH STREET, SUITE 4700, LOS ANGELES, CA, 90071
NUMBER OF CLAIMS: 20
EXEMPLARY CLAIM: 1
LINE COUNT: 3380
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention includes a basic method for discovering the function of gene and their corresponding gene products relative to a specific biological process or physiological condition. The invention provides the ability to develop therapeutic and diagnostic agents using the information obtained from the practice of the basic method. In the method, the gene product of a selected polynucleotide is delivered to a mammal to provide an immune response. The polynucleotide sequences may express, in vivo by immunization of an animal, or in bacterial system or other known system for expression of a polynucleotide sequence. The sera resulting from immunization with the gene product contains antibodies to

the gene product which are used in function determinative assays to determine the function of the gene sequence gene product relative to a biological process or physiological condition, typically a disease in a human. The information derived from the function determinative assay enables the discovery of novel genes and gene products and provides the ability to design and/or manufacture of therapeutic or diagnostic products based on the practice of the basic methodology of the invention.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L69 ANSWER 39 OF 64 USPATFULL on STN
ACCESSION NUMBER: 2002:48606 USPATFULL
TITLE: Irrigation solution and method for inhibition of pain and inflammation
INVENTOR(S): Demopulos, Gregory A., Mercer Island, WA, UNITED STATES
Pierce-Palmer, Pamela, San Francisco, CA, UNITED STATES
Herz, Jeffrey M., Mill Creek, WA, UNITED STATES
PATENT ASSIGNEE(S): Omeros Medical Systems (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2002028798	A1	20020307
APPLICATION INFO.:	US 2001-839633	A1	20010420 (9)

RELATED APPLN. INFO.: Continuation-in-part of Ser. No. WO 1999-US24625, filed on 20 Oct 1999, UNKNOWN Continuation-in-part of Ser. No. WO 1999-US24672, filed on 20 Oct 1999, UNKNOWN Continuation-in-part of Ser. No. WO 1999-US24558, filed on 20 Oct 1999, UNKNOWN Continuation-in-part of Ser. No. WO 1999-US24557, filed on 20 Oct 1999, UNKNOWN Continuation-in-part of Ser. No. WO 1999-US26330, filed on 5 Nov 1999, UNKNOWN Continuation-in-part of Ser. No. US 1998-72913, filed on 4 May 1998, UNKNOWN Continuation of Ser. No. US 1996-670699, filed on 26 Jun 1996, UNKNOWN Continuation-in-part of Ser. No. WO 1995-US16028, filed on 12 Dec 1995, UNKNOWN Continuation-in-part of Ser. No. US 1994-353775, filed on 12 Dec 1994, ABANDONED

	NUMBER	DATE
PRIORITY INFORMATION:	US 1998-105026P	19981020 (60)
	US 1998-105029P	19981020 (60)
	US 1998-105044P	19981020 (60)
	US 1998-105166P	19981021 (60)
	US 1998-107256P	19981105 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: CHRISTENSEN, O'CONNOR, JOHNSON, KINDNESS, PLLC, 1420 FIFTH AVENUE, SUITE 2800, SEATTLE, WA, 98101-2347
NUMBER OF CLAIMS: 19
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 12 Drawing Page(s)
LINE COUNT: 4713
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB A method and solution for perioperatively inhibiting a variety of pain and inflammation processes at wounds from general surgical procedures including oral/dental procedures. The solution preferably includes at least one pharmacological agent selected from the group consisting of a mitogen-activated protein kinase (MAPK) inhibitor, an α.sub.2-receptor agonist, a neuronal nicotinic acetylcholine receptor agonist, a cyclooxygenase-2 (COX-2) inhibitor, a soluble receptor and mixtures thereof, and optionally additional multiple pain and inflammation inhibitory agents at dilute concentration in a physiologic carrier, such as saline or lactated Ringer's solution. The solution is applied by continuous irrigation of a wound during a

surgical procedure for preemptive inhibition of pain and while avoiding undesirable side effects associated with oral, intramuscular, subcutaneous or intravenous application of larger doses of the agents.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L69 ANSWER 40 OF 64 USPATFULL on STN
ACCESSION NUMBER: 2002:42957 USPATFULL
TITLE: Composition for the prevention and/or treatment of atherosclerosis
INVENTOR(S): Shoenfeld, Yehuda, Ramat Gan, ISRAEL
Harats, Dror, Ramat Gan, ISRAEL
George, Jacob, Petah Tikva, ISRAEL

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2002025321	A1	20020228
APPLICATION INFO.:	US 2001-944592	A1	20010904 (9)

RELATED APPLN. INFO.: Continuation of Ser. No. US 2001-806400, filed on 30 Mar 2001, UNKNOWN

	NUMBER	DATE
PRIORITY INFORMATION:	IL 1998-126447	19981004

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: SOL SHEINBEIN, c/o ANTHONY CASTORINA, SUITE 207, 2001 JEFFERSON DAVIS HIGHWAY, ARLINGTON, VA, 22202
NUMBER OF CLAIMS: 26
EXEMPLARY CLAIM: 1
LINE COUNT: 977
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB An immunological oral tolerance-inducing composition for prevention and/or treatment of atherosclerosis, comprising an active component selected from the group consisting of modified low density lipoprotein, oxidized low density lipoprotein (Ox LDL), heat shock protein 60/65 (HSP 60/65), beta.sub.2-glycoprotein-1(β.sub.2GP-1), functional derivatives thereof and mixtures thereof, in combination with a pharmaceutically acceptable carrier for oral administration.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L69 ANSWER 41 OF 64 USPATFULL on STN
ACCESSION NUMBER: 2002:291078 USPATFULL
TITLE: Polynucleotides and polypeptides derived from corn ear
INVENTOR(S): Lalgudi, Raghunath V., Clayton, MO, United States
Ito, Laura Y., Pleasanton, CA, United States
Sherman, Bradley K., Oakland, CA, United States
PATENT ASSIGNEE(S): Incyte Genomics, Inc., Palo Alto, CA, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 6476212	B1	20021105
APPLICATION INFO.:	US 1999-313294		19990514 (9)

	NUMBER	DATE
PRIORITY INFORMATION:	US 1998-86722P	19980526 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: GRANTED
PRIMARY EXAMINER: Brusca, John S.
ASSISTANT EXAMINER: Moran, Marjorie A.
LEGAL REPRESENTATIVE: Incyte Genomics, Inc., Murry, Lynn E.
NUMBER OF CLAIMS: 5
EXEMPLARY CLAIM: 1

NUMBER OF DRAWINGS: 0 Drawing Figure(s); 0 Drawing Page(s)
LINE COUNT: 23084
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention provides purified, corn ear-derived polynucleotides (cdps) which encode corn ear-derived polypeptides (CDPs). The invention also provides for the use of cdps or their complements, oligonucleotides, or fragments in methods for determining altered gene expression, to recover regulatory elements, and to follow inheritance of desirable characteristics through hybrid breeding programs. The invention further provides for vectors and host cells containing cdps for the expression of CDPs. The invention additionally provides for (i) use of isolated and purified CDPs to induce antibodies and to screen libraries of compounds and (ii) use of anti-CDP antibodies in diagnostic assays.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L69 ANSWER 42 OF 64 PASCAL COPYRIGHT 2004 INIST-CNRS. ALL RIGHTS RESERVED. on STN
ACCESSION NUMBER: 2002-0359879 PASCAL
COPYRIGHT NOTICE: Copyright .COPYRGT. 2002 INIST-CNRS. All rights reserved.
TITLE (IN ENGLISH): Neuroprotective effects of hyperthermic preconditioning on infarcted volume after middle cerebral artery occlusion in rats: Role of adenosine receptors
AUTHOR: HUI XU; AIBIKI Mayuki; NAGOYA Junko
CORPORATE SOURCE: Department of Anesthesiology and Emergency Medicine and the Intensive Care Unit, Kagawa Medical University, 1750-1, Ikenobe, Miki, Kita, Kagawa 761-0793, Japan
SOURCE: Critical care medicine, (2002), 30(5), 1126-1130, 22 refs.
ISSN: 0090-3493 CODEN: CCMDC7
DOCUMENT TYPE: Journal
BIBLIOGRAPHIC LEVEL: Analytic
COUNTRY: United States
LANGUAGE: English
AVAILABILITY: INIST-17751, 354000101335600270
AN 2002-0359879 PASCAL
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AB Objective: There are still only a limited number of studies regarding the neuroprotective effects of hyperthermic preconditioning on regional brain ischemia or regarding the role of adenosine A1 receptors in such pretreatment. We examined the effects of hyperthermic pretreatment on infarcted volume after middle cerebral artery occlusion (MCAO), as well as the contribution of A1 receptors, to the responses in rats. Design: Prospective, randomized animal study. Settings: An animal research laboratory in a medical university. Subjects: Male Wistar rats (200-250 g). Intervention: All animals were anesthetized with isoflurane during each pretreatment, as well as for MCAO. The animals were assigned as follows: (i) sham-control group (n = 8), which was maintained at normothermia (37 ± 0.2°C pericranial temperature) for 15 mins, then kept in an awake state for 0.5, 3, 6, 18, 24, or 48 hrs before 2-hr MCAO; (ii) hyperthermia group (n = 8), which was subjected to 42 ± 0.5°C for 15 mins, and then received the same treatment as the sham group; (iii) DPCPX (a selective central adenosine receptor antagonist)-treated control group, which was given the agent before normothermia pretreatment, then kept for a recovery time of 0.5 or 24 hrs (n = 8 in each group) before MCAO; (iv) DPCPX plus hyperthermia-treated group, which was **administered** the agent at the same dose as the control before hyperthermic exposure, then selected for each recovery time (n = 8 in each group) before MCAO; (v) DPCPX-ischemic group, to which the agent was **administered** before MCAO (n = 8); and (vi) vehicle-ischemic group, in which peanut oil as a vehicle, instead of DPCPX, was injected before MCAO (n = 8). Values are expressed as mean

± SE. Statistical analysis was done by analysis of variance, followed by Scheffe's F test, Mann-Whitney U test, or the chi-square test as appropriate (p <.05). Main Results: The infarcted volume in hyperthermic animals kept for 18 or 24 hrs before the occlusion procedure was significantly smaller than in the sham controls, but not in rats kept for 0.5, 3.0, 6.0, and 48 hrs. DPCPX partially reversed the reduction in infarcted volume that was induced by hyperthermic preconditioning after focal ischemia, whereas the agent itself did not affect the volume after ischemia. Conclusion: These data indicate that hyperthermic pretreatment reduces the effects on MCAO-induced cerebral infarction, possibly via a partial mediation of the central adenosine receptors in the brain. The results also suggest a need for further studies to define the relationship between **heat shock proteins** and central adenosine receptors in preconditioning.

L69 ANSWER 43 OF 64 PASCAL COPYRIGHT 2004 INIST-CNRS. ALL RIGHTS RESERVED. on STN

ACCESSION NUMBER: 2002-0455958 PASCAL
COPYRIGHT NOTICE: Copyright .COPYRGT. 2002 INIST-CNRS. All rights reserved.
TITLE (IN ENGLISH): Effects of normobaric hyperoxia in a rat model of focal cerebral ischemia-reperfusion
AUTHOR: SINGHAL Aneesh B.; XIAOYING WANG; SUMII Toshihisa; MORI Tatsuro; LO Eng H.
CORPORATE SOURCE: Neuroprotection Research Laboratory, Departments of Neurology and Radiology, Massachusetts General Hospital, Charlestown, Massachusetts, United States; Program in Neuroscience, Harvard Medical School, Boston, Massachusetts, United States
SOURCE: Journal of cerebral blood flow and metabolism, (2002), 22(7), 861-868, 41 refs.
ISSN: 0271-678X CODEN: JCBMDN
DOCUMENT TYPE: Journal
BIBLIOGRAPHIC LEVEL: Analytic
COUNTRY: United States
LANGUAGE: English
AVAILABILITY: INIST-19142, 354000105096110110
AN 2002-0455958 PASCAL
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AB Recent studies suggest that normobaric hyperoxia can be beneficial, if **administered** during transient stroke. However, increased oxygenation theoretically may increase oxygen free-radical injury, particularly during reperfusion. In the present study, the authors assessed the benefit and risks of hyperoxia during focal cerebral ischemia and reperfusion. Rats were subjected to hyperoxia (FIO.sub.2 100%) or normoxia (FIO.sub.2 30%) during 2-hour filament occlusion and I-hour reperfusion of the middle cerebral artery. At 24 hours, the hyperoxia group showed 70% (total) and 92% (cortical) reduction in infarct volumes as compared to the normoxia group. Levels of oxidative stress were evaluated using three indirect methods. First, since oxygen free radicals increase blood-brain barrier (BBB) damage, Evan's blue dye extravasation was quantified to assess BBB damage. Second, the expression of heme oxygenase-1 (HO-1), a **heat shock protein** inducible by oxidative stress, was assessed using Western blot techniques. Third, an immunoblot technique ("OxyBlot") was used to assess levels of protein carbonyl formation as a marker of oxidative stress-induced protein denaturation. At 24 hours, Evan's blue dye extravasation per average lesion volume was similar between groups. There were no significant differences in HO-I induction and protein carbonyl formation between groups, in the ipsilateral or contralateral hemispheres, at 6 hours and at 24 hours. These results indicate that hyperoxia treatment during focal cerebral ischemia-reperfusion is neuroprotective, and does not increase oxidative stress.

L69 ANSWER 44 OF 64 JICST-EPlus COPYRIGHT 2004 JST on STN
ACCESSION NUMBER: 1030126864 JICST-EPlus

TITLE: The effects of Kampo herbal medicines (Scutellariae Radix, Carthami Flos, Linderae Radix) on the atherosclerosis mouse model introduced with heat shock protein (Hsp) 60 and high cholesterol diet.

AUTHOR: TOMII M
SONG Q-H
MORI Y
CYONG J-C

CORPORATE SOURCE: Univ. Tokyo, Tokyo, Jpn
Koshigaya Hospital Of Dokkyo Medical Univ., Saitama, Jpn
Tomii Clinic, Shizuoka, Jpn
Juntendo Univ., Tokyo, Jpn

SOURCE: Wakan Iyakugaku Zasshi (Journal of Traditional Medicines), (2002) vol. 19, no. 6, pp. 216-222. Journal Code: Y0941A (Fig. 4, Tbl. 2, Ref. 23)
ISSN: 1340-6302

PUB. COUNTRY: Japan
DOCUMENT TYPE: Journal; Article
LANGUAGE: English
STATUS: New

AB In the process of the formation of atherosclerosis, many immune factors, such as cytokines and chemokines are involved. On the other hand, **heat shock proteins** (Hsps) work as a Chaperon and are considered to have an effect that protects the cell from protein damage by restoration of the degenerated proteins. We were successfull in establishing an atherosclerosis mouse model in C57BL/6NJc mice immunized with Hsp60 and simultaneously treated with a high cholesterol diet (HCD). At this time, using this model, we verified the effects of Kampo herbal medicines, Scutellariae Radix (SR), Carthami Flos (CF) and Linderae Radix (LR), on the pathological atherosclerositic change in the aorta, change in body weight, and alteration of serum cytokine levels. At first, compared with the control group, the reduction in the body weight of the groups that was **administered** with SR and CF were suppressed significantly ($p<0.05$). On the other hand, the production of IFN-Γ of the groups that were **administered** with SR and CF were suppressed significantly, but the LR group only showed a tendency of suppression. The lipid deposits that we observed have a tendency to increase the volume and area gradually from the aortic valve to the root of ascending aorta. The deposits were observed in each mouse of the control group and SR group, but only 20 to 60% of the mice in the remaining groups (CF group and LR group) exhibited lipid deposition. Consequently we found that the herbal medicines reduced the adjuvant function of Hsp60, and simultaneously reduced the progression of the atheroscleosis. (author abst.)

L69 ANSWER 45 OF 64 CAPLUS COPYRIGHT 2004 ACS on STN DUPLICATE 5

ACCESSION NUMBER: 2001:693117 CAPLUS
DOCUMENT NUMBER: 135:251960

TITLE: Suppression of **vascular disorders** by mucosal administration of heat shock protein peptides

INVENTOR(S): Weiner, Howard L.; Maron, Ruth; Libby, Peter
PATENT ASSIGNEE(S): Brigham and Women's Hospital, Inc., USA

SOURCE: PCT Int. Appl., 49 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001068124	A2	20010920	WO 2001-US8351	20010315
WO 2001068124	A3	20020314		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM,

HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS,
LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO,
RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN,
YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY,
DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF,
BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG
PRIORITY APPLN. INFO.: US 2000-189855P P 20000315
AB Methods are disclosed for treating **vascular disorders** in mammals. The methods involve **administering** one or more agents selected from a **heat shock protein**, a therapeutically effective fragment and a therapeutically effective analog of a **heat shock protein** in a form suitable for mucosal administration. In some embodiments the heat shock protein of the method is mycobacterial HSP65. In some embodiments the heat shock protein is human HSP60. In some embodiments the heat shock protein is chlamydial HSP60. The method is of particular value in the treatment of atherosclerosis. Also disclosed are compns. useful for treating **vascular disorders** in mammals. The compns. include one or more agents selected from heat shock protein, therapeutically effective fragments and therapeutically effective analogs of the heat shock protein in aerosol or oral form. In some embodiments the heat shock protein of the composition is mycobacterial HSP65. In some embodiments the heat shock protein of the method is human HSP60. In some embodiments the heat shock protein is chlamydial HSP60. The compns. is of particular value in the treatment of atherosclerosis.

L69 ANSWER 46 OF 64 USPATFULL on STN DUPLICATE 6
ACCESSION NUMBER: 2001:182581 USPATFULL
TITLE: Methods for delivering compounds into a cell
INVENTOR(S): Unger, Evan C., Tucson, AZ, United States
McCreery, Thomas, Tucson, AZ, United States
PATENT ASSIGNEE(S): ImaRX Pharmaceutical Corporation (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2001031740	A1	20011018
	US 6638767	B2	20031028
APPLICATION INFO.:	US 2000-742938	A1	20001221 (9)

RELATED APPLN. INFO.: Division of Ser. No. US 1997-841169, filed on 29 Apr 1997, PENDING Continuation-in-part of Ser. No. US 1997-785661, filed on 17 Jan 1997, ABANDONED Continuation-in-part of Ser. No. US 1996-640554, filed on 1 May 1996, ABANDONED
DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: Woodcock Washburn Kurtz, MacKiewicz & Norris LLP, One Liberty Place - 46th Floor, Philadelphia, PA, 19103
NUMBER OF CLAIMS: 104
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 7 Drawing Page(s)
LINE COUNT: 2971
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention is directed, inter alia, to a method for delivering a compound into a cell comprising administering to the cell the compound to be delivered, an organic halide, and/or a carrier. Ultrasound may also be applied, if desired.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L69 ANSWER 47 OF 64 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 2002:95551 BIOSIS
DOCUMENT NUMBER: PREV200200095551
TITLE: Pharmacological preconditioning with low-dose cyclosporine or FK506 reduces subsequent ischemia/reperfusion injury in rat kidney.

AUTHOR(S): Yang, Chul Woo; Ahn, Hee Jong; Han, Hyuk Joon; Kim, Wan Young; Li, Can; Shin, Mi Jung; Kim, Sung Kwon; Park, Joo Hyun; Kim, Yong Soo; Moon, In Sung; Bang, Byung Kee [Reprint author]
CORPORATE SOURCE: Department of Internal Medicine, Kangnam St. Mary's Hospital, Catholic University of Korea, 505 Banpo-Dong, Seocho-Ku, Seoul, 137-040, South Korea
SOURCE: Transplantation (Baltimore), (December 15, 2001) Vol. 72, No. 11, pp. 1753-1759. print.
CODEN: TRPLAU. ISSN: 0041-1337.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 24 Jan 2002
Last Updated on STN: 25 Feb 2002

AB Background: Ischemia/reperfusion (I/R) injury in the early posttransplant period is closely associated with delayed recovery of graft function, increased acute rejection, and late allograft dysfunction. Pharmacological preconditioning with low-dose cyclosporine (CsA) or FK506 was performed to induce ischemic tolerance in rat kidney with I/R injury. Methods: Low-dose CsA (3 mg/kg, **administered** i.v.) or FK506 (0.3 mg/kg i.v.) were used to induce ischemic tolerance in Sprague-Dawley rats, and the induction of **heat shock protein** (hsp) 70 by CsA or FK506 was evaluated overtime. Rats were pretreated with CsA or FK506 6 hr before I/R injury when hsp70 was maximally expressed, and were killed 24 hr later. The effect of pharmacological preconditioning on subsequent I/R injury was evaluated in terms of renal function, histopathology score, assays for apoptosis (DNA fragmentation analysis, TUNEL staining, expressions of pro-apoptotic genes, and caspase activity), and the expression of inflammatory cytokine genes (interleukin-1 and tumor necrosis factor-alpha). Results: Preconditioning with low-dose CsA or FK506 significantly improved renal function and renal histology, compared to rats with I/R injury. Apoptotic cell death (typical DNA laddering and increased TUNEL-positive cells) in rat kidneys with I/R injury, was decreased by pretreatment with low-dose CsA or FK506. Increased expression of pro-apoptotic genes (Fas, Fas-ligand, caspase 1 and 3) and activated caspases in ischemic rat kidneys were decreased after CsA or FK506 pretreatment. Conclusions: Pretreatment with low-dose CsA or FK506 prevents subsequent I/R injury, and this effect may be related to the induction of hsp70. Pretreatment of renal donors with low-dose CsA or FK506 may result in an improvement in immediate posttransplant function.

L69 ANSWER 48 OF 64 BIOTECHNO COPYRIGHT 2004 Elsevier Science B.V. on STN
DUPLICATE
ACCESSION NUMBER: 2001:34036899 BIOTECHNO
TITLE: A radicicol derivative, KF58333, inhibits expression of hypoxia-inducible factor-1α and vascular endothelial growth factor, angiogenesis and growth of human breast cancer xenografts
AUTHOR: Kurebayashi J.; Otsuki T.; Kurosumi M.; Soga S.; Akinaga S.; Sonoo H.
CORPORATE SOURCE: J. Kurebayashi, Department of Breast, Kawasaki Medical School, 577 Matsushima, Kurashiki, Okayama 701-0192, Japan.
E-mail: kure@med.kawasaki-m.ac.jp
SOURCE: Japanese Journal of Cancer Research, (2001), 92/12 (1342-1351), 37 reference(s)
CODEN: JJCREP ISSN: 0910-5050
DOCUMENT TYPE: Journal; Article
COUNTRY: Japan
LANGUAGE: English
SUMMARY LANGUAGE: English

AN 2001:34036899 BIOTECHNO
AB A novel oxime derivative of radicicol, KF58333, binds to the **heat shock protein** 90 (Hsp90) and destabilizes its associated signaling molecules. These effects play a critical role in the growth inhibition of tumor cells. To further investigate the effects of

this agent, it was **administered** to two human breast cancer cell lines, KPL-1 and KPL-4, both in vitro and in vivo. KF58333 dose-dependently inhibited the growth and **vascular** endothelial growth factor (VEGF) secretion, concomitantly with a decrease in VEGF mRNA expression, in each cell line. This agent also suppressed the increase of VEGF secretion and expression induced by hypoxia (1% O.sub.2). Intravenous injections of this agent into nude mice bearing either KPL-1 or KPL-4 xenografts significantly inhibited the tumor growth associated with a decrease in the Ki67 labeling index and microvascular area and an increase in apoptosis and the necrotic area. These findings indicate that the antitumor activity of this radicicol derivative may be partly mediated by decreasing VEGF secretion from tumor cells and inhibiting tumor angiogenesis. To explore the action mechanisms of the anti-angiogenic effect, the expression level of hypoxia-inducible factor (HIF)-1α was investigated. KF58333 provided a significant decrease in the HIF-1α protein expression under both normoxic and hypoxic **conditions**. In contrast, the mRNA expression of HIF-1α was not decreased by this agent. It is suggested that the post-transcriptional down-regulation of HIF-1α expression by this agent may result in a decrease of VEGF expression and tumor angiogenesis.

L69 ANSWER 49 OF 64 PASCAL COPYRIGHT 2004 INIST-CNRS. ALL RIGHTS RESERVED. on STN

ACCESSION NUMBER: 2001-0208807 PASCAL
COPYRIGHT NOTICE: Copyright .COPYRGT. 2001 INIST-CNRS. All rights reserved.
TITLE (IN ENGLISH): Thermotolerance protects against endotoxin-mediated microvascular injury
AUTHOR: GANG CHEN; KELLY Cathal; HONG CHEN; LEAHY Austin; BOUCHIER-HAYES David
CORPORATE SOURCE: Surgical Research Laboratory, Department of Surgery, Royal College of Surgeons in Ireland, Beaumont Hospital, Dublin, Ireland
SOURCE: The Journal of surgical research, (2001), 95(2), 79-84, 32 refs.
Conference: Annual Meeting of the Association for Academic Surgery, Philadelphia, Pennsylvania (United States), 18 Nov 1999
ISSN: 0022-4804 CODEN: JSGRA2
DOCUMENT TYPE: Journal; Conference
BIBLIOGRAPHIC LEVEL: Analytic
COUNTRY: United States
LANGUAGE: English
AVAILABILITY: INIST-9554, 354000098766170010

AN 2001-0208807 PASCAL
CP Copyright .COPYRGT. 2001 INIST-CNRS. All rights reserved.
AB An early event in endotoxin-induced tissue injury is adhesion and migration of leukocytes through the endothelium. This is a three-stage process, initially low-grade selectin-mediated adhesion, seen as a decrease in rolling velocity, followed by integrin-mediated adhesion and transmigration. Thermotolerance has been shown to reduce tissue injury and mortality induced by endotoxin. The aim of this study was to investigate the effect of thermotolerance on leukocyte-endothelial interactions. Intravital video microscopy was used to examine hemodynamic parameters, leukocyte rolling, adhesion, and migration in rat mesenteric postcapillary venules. Sprague-Dawley rats were randomized into control, lipopolysaccharide (LPS), and thermotolerance + LPS groups. Thermotolerance was induced 18 h prior to administration of LPS by elevating core body temperature to 41 + 0.5°C for 15 min. LPS (055:B5 15 mg/kg) was **administered** via the jugular vein after baseline recording. Leukocyte rolling velocity and the number of adherent and migrated leukocytes were measured by intravital microscopy at baseline 0 min and 10, 30, 60, and 90 min after LPS administration. **Heat shock protein** 72 (HSP72) expression in tissues was determined by Western immunoblotting. The results indicated that LPS administration significantly decreased leukocyte rolling

velocity during endotoxemia and increased leukocyte adhesion (10.3 ± 1.67, 13.2 ± 1.40, and 10.0 ± 1.57/100 μm) and migration (5.7 ± 1.02 and 8.3 ± 1.76/field) at 30, 60, and 90 min after LPS injection ($P < 0.01$ vs baseline and control group). Thermotolerance maintained leukocyte rolling velocity and significantly reduced leukocyte adhesion (5.7 ± 0.88 and 4.0 ± 0.68/100 μm) and migration (2.8 ± 0.32 and 3.0 ± 0.68/field) at 30 and 60 min after LPS administration ($P < 0.01$ and 0.05 vs LPS group). Expression of HSP72 was induced in mesentery, gut, and lung by thermotolerance. This study indicates that thermotolerance attenuated LPS-induced microvascular injury by decreasing leukocyte-endothelial adhesion and migration.

L69 ANSWER 50 OF 64 USPATFULL on STN
ACCESSION NUMBER: 2000:160598 USPATFULL
TITLE: Vaccine compositions and methods useful in inducing immune protection against arthritogenic peptides involved in the pathogenesis of rheumatoid arthritis
INVENTOR(S): Carson, Dennis A., Del Mar, CA, United States
Albani, Salvatore, Encinitas, CA, United States
PATENT ASSIGNEE(S): The Regents of the University of California, Oakland, CA, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 6153200		20001128
APPLICATION INFO.:	US 1998-107615		19980630 (9)

RELATED APPLN. INFO.: Division of Ser. No. US 1996-618464, filed on 15 Mar 1996, now patented, Pat. No. US 5773570 which is a continuation-in-part of Ser. No. US 1994-246988, filed on 20 May 1994, now abandoned
DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Minnifield, Nita
LEGAL REPRESENTATIVE: Gates & Cooper
NUMBER OF CLAIMS: 8
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 5 Drawing Figure(s); 5 Drawing Page(s)
LINE COUNT: 1073
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Vaccine compositions useful in inducing immune protection in a host against arthritogenic peptides involved in the pathogenesis of rheumatoid arthritis are disclosed. Each vaccine composition provides antigenic dnaJp1 peptide (by including the peptide or a polynucleotide which encodes the peptide) and, optionally, other peptide fragments of the microbial dnaJ protein and/or human homologs thereof. Methods for identifying persons who are predisposed to develop rheumatoid arthritis and methods for use of the inventive vaccines are also disclosed.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L69 ANSWER 51 OF 64 PASCAL COPYRIGHT 2004 INIST-CNRS. ALL RIGHTS RESERVED. on STN
ACCESSION NUMBER: 2000-0150806 PASCAL
COPYRIGHT NOTICE: Copyright .COPYRGT. 2000 INIST-CNRS. All rights reserved.
TITLE (IN ENGLISH): Differential role of nitric oxide pathway and heat shock protein in preconditioning and lipopolysaccharide-induced brain ischemic tolerance
AUTHOR: PUISIEUX F.; DEPLANQUE D.; QIAN PU; SOUIL E.; BASTIDE M.; BORDET R.
CORPORATE SOURCE: Laboratoire de Pharmacologie, Faculte de Medecine Henri Warembourg, Pole Recherche, 1 Place de Verdun, 59045 Lille, France; Laboratoire de Biologie, Physiologie et Pathologie de la Respiration, CHU Cochin AP-HP Universite Paris V, 24 rue du Faubourg Saint-Jacques, 75014 Paris, France

SOURCE: European journal of pharmacology, (2000), 389(1), 71-78, 32 refs.
ISSN: 0014-2999 CODEN: EJPHAZ
DOCUMENT TYPE: Journal
BIBLIOGRAPHIC LEVEL: Analytic
COUNTRY: Netherlands
LANGUAGE: English
AVAILABILITY: INIST-13322, 354000086625130090
AN 2000-0150806 PASCAL
CP Copyright .COPYRGT. 2000 INIST-CNRS. All rights reserved.
AB The purposes of this study were to investigate the role of nitric oxide (NO), nitric oxide synthase (NOS), and 70 kDa **heat shock protein** in brain ischemic tolerance induced by ischemic preconditioning and lipopolysaccharide. Focal cerebral ischemia was induced in rats by intraluminal middle cerebral artery occlusion. Infarct volume was significantly reduced (1) in rats subjected to 3 min ischemia 72 h prior to 60 min ischemia; (2) in rats **administered** lipopolysaccharide (0.5 mg/kg; i.p.) 72 h prior to 60 min ischemia compared with controls. The beneficial effect of ischemic preconditioning was unchanged despite prior administration of nitro-L-arginine methyl ester (L-NAME), a NOS inhibitor. Conversely, the protective effect of lipopolysaccharide was nullified by L-NAME. Using immunohistochemical techniques, we observed that (1) ischemic preconditioning but not lipopolysaccharide induces the expression of 70 kDa **heat shock protein** in cerebral cortex and (2) lipopolysaccharide induces early increased expression of endothelial NOS in cerebral blood vessels. The results suggest that (1) endothelium-derived NO plays a role of a trigger in the brain tolerance induced by lipopolysaccharide, and (2) 70 kDa **heat shock protein** is involved in the protection afforded by ischemic preconditioning but not by lipopolysaccharide.

L69 ANSWER 52 OF 64 PASCAL COPYRIGHT 2004 INIST-CNRS. ALL RIGHTS RESERVED. on STN
ACCESSION NUMBER: 2000-0158096 PASCAL
COPYRIGHT NOTICE: Copyright .COPYRGT. 2000 INIST-CNRS. All rights reserved.
TITLE (IN ENGLISH): Possible role of the superoxide anion in the development of neuronal tolerance following ischaemic preconditioning in rats
AUTHOR: MORI T.; MURAMATSU H.; MATSUI T.; MCKEE A.; ASANO T.
CORPORATE SOURCE: Institute of Laboratory Animal Science, Saitama Medical Center/School, Saitama, Japan; Department of Internal Medicine, Saitama Medical Center/School, Saitama, Japan; Department of Neurosurgery, Saitama Medical Center/School, Saitama, Japan; Second Department of Pathology, Nippon Medical School, Tokyo, Japan
SOURCE: Neuropathology and applied neurobiology, (2000), 26(1), 31-40, 40 refs.
ISSN: 0305-1846 CODEN: NANEDL
DOCUMENT TYPE: Journal
BIBLIOGRAPHIC LEVEL: Analytic
COUNTRY: United Kingdom
LANGUAGE: English
AVAILABILITY: INIST-17534, 354000086778340040
AN 2000-0158096 PASCAL
CP Copyright .COPYRGT. 2000 INIST-CNRS. All rights reserved.
AB There is a large body of evidence that reactive oxygen species play a major role in the pathogenesis of ischaemic brain damage. On the other hand, it has recently been suggested that superoxide anions participate in the development of neuronal tolerance against lethal ischaemia following ischaemic preconditioning (PC). The present study aimed to examine whether or not the intravenous administration of human recombinant Cu/Zn superoxide dismutase (hr SOD) prior to PC would affect the subsequent development of neuronal tolerance. Animals were randomly

assigned to the following three groups: group 1, sham PC treated with vehicle; group 2, PC treated with hr SOD and group 3, PC treated with vehicle. For PC, 10 min occlusion of the middle cerebral artery (MCA) by a modified intraluminal suture method was followed by 60 min recirculation and this procedure was successively repeated three times. The procedures were similar for sham PC except that the MCA was kept unoccluded. Just prior to PC or sham PC, a bolus of hr SOD (6 x 10.sup.3 IU/2 ml/kg) was **administered** intravenously. Seventy-two hours thereafter, rats were subjected to lethal ischaemia, i.e. MCA occlusion for 100 min followed by recirculation for 48 h. The infarct area and volume were assessed with the 2,3,5-triphenyltetrazolium stain. A significant difference in the infarct volume was revealed between the sham PC/vehicle and the PC/vehicle groups (total and cortex $P < 0.01$; striatum $P < 0.05$), showing that PC induced a marked neuronal tolerance against lethal ischaemia. The infarct volume in the PC/SOD group was close to that in the sham PC/vehicle group, being significantly greater than that in the PC/vehicle group (total and cortex $P < 0.01$) and showing that the administration of hr SOD suppressed the development of neuronal tolerance induced by PC. In a parallel experiment, expression of 72-kDa **heat-shock protein** (hsp 72) at 72 h after PC was considerably reduced in rats treated with hr SOD compared with those treated with vehicle. These results suggest that superoxide anions intraluminally generated within cerebral microvessels participate in the development of neuronal tolerance as well as the induction of hsp 72 following PC.

L69 ANSWER 53 OF 64 PASCAL COPYRIGHT 2004 INIST-CNRS. ALL RIGHTS RESERVED. on STN

ACCESSION NUMBER:	2000-0064326 PASCAL
COPYRIGHT NOTICE:	Copyright .COPYRGT. 2000 INIST-CNRS. All rights reserved.
TITLE (IN ENGLISH):	Differential expression pattern of heme oxygenase-1/heat shock protein 32 and nitric oxide synthase-II and their impact on liver injury in a rat model of hemorrhage and resuscitation
AUTHOR:	RENSING H.; BAUER I.; DATENE V.; PAETAU C.; PANNEN B. H. J.; BAUER M.
CORPORATE SOURCE:	Department of Anesthesiology and Critical Care Medicine, University of the Saarland, Homburg, Germany, Federal Republic of; Department of Anesthesiology and Critical Care Medicine, University of Freiburg, Freiburg, Germany, Federal Republic of
SOURCE:	Critical care medicine, (1999), 27(12), 2766-2775, 50 refs. ISSN: 0090-3493 CODEN: CCMDC7
DOCUMENT TYPE:	Journal
BIBLIOGRAPHIC LEVEL:	Analytic
COUNTRY:	United States
LANGUAGE:	English
AVAILABILITY:	INIST-17751, 354000081295880270

AN 2000-0064326 PASCAL

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AB Objective: To investigate the role of the vasodilator systems heme oxygenase-1/**heat shock protein** 32 (HO-1/HSP32) and nitric oxide synthase-II (NOS-II), generating carbon monoxide and nitric oxide respectively, as modulators of liver injury in an experimental model of reversible hemorrhagic shock. Design: Prospective controlled laboratory study. Setting: University research laboratory. Subjects: Male Sprague-Dawley rats weighing 250-350 g. Interventions: Animals were anesthetized and assigned to a hemorrhagic shock (mean arterial pressure, 35-40 mmHg for 60 mins) or a sham protocol. On the basis of the time course of gene expression, HO-1/HSP32 or NOS-II was blocked 5 hrs after onset of resuscitation. To assess the role of the antioxidative properties of the heme oxygenase (HO) pathway in additional experiments, Trolox, a potent antioxidant, was **administered** at the time of blockade of HO. Liver injury was

assessed morphometrically and by plasma α-glutathione-S-transferase (α-GST) release 11 hours after onset of resuscitation. Measurements and Main Results: Hemorrhage and resuscitation increased HO-1/HSP32 messenger RNA and protein primarily in parenchymal cells, and a faint induction of NOS-II, restricted to nonparenchymal cells, was observed. Inhibition of the HO paths way with tin protoporphyrin-IX (SnPP-IX) increased the incidence of pericentral necrosis (intact acini: shock/vehicle 68.8%; shock/ SnPP-IX 42.6%) and α-GST levels (sham 94 ± 24 μg/L; shock/ vehicle 377 ± 139 μg/L; shock/SnPP-IX 1708 ± 833 μg/L), whereas blockade of NOS-II with S-methylisothiourea did not affect liver injury. Coadministration of Trolox failed to attenuate the aggravation of necrosis associated with blockade of HO, whereas α-GST levels were reduced (intact acini: shock/vehicle/ Trolox 82.1%, shock/SnPP-IX/Trolox 42.7%; α-GST: shock/vehicle/Trolox 202 ± 55 μg/L; shock/SnPP-IX/Trolox 236 ± 61 μg/L). Conclusions: These data suggest that HO-1/HSP32, but not the alternative cyclic guanosine monophosphate-generating enzyme NOS-II, is induced after hemorrhage and resuscitation and protects against hepatocellular injury. Both metabolites generated by the heme oxygenase pathway, e.g., carbon monoxide (a vasodilator) and biliverdin (an antioxidant) seem to contribute to the salutary effects of induction of HO-1/HSP32.

L69 ANSWER 54 OF 64 PASCAL COPYRIGHT 2004 INIST-CNRS. ALL RIGHTS RESERVED. on STN

ACCESSION NUMBER: 2000-0017130 PASCAL
COPYRIGHT NOTICE: Copyright .COPYRGT. 2000 INIST-CNRS. All rights reserved.
TITLE (IN ENGLISH): Myocardial protection with monophosphoryl lipid-A against aortic cross clamping-induced global stunning
AUTHOR: ABD-ELFATTAH A. S. A.; GUO J.-H.; SHI PING GOA; ELLIOT G. A.; WEBER P.; MAHGOUB M. A.; MARKTANNER R.; MOHAMED A.
CORPORATE SOURCE: Department of Surgery, Department of Pharmacology and Toxicology, and Department of Emergency Medicine, Medical College of Virginia, Virginia Commonwealth University, Richmond, Virginia, United States
SOURCE: The Annals of thoracic surgery, (1999), 68(5), 1954-1959, 34 refs.
Conference: International Symposium on Myocardial Protection From Surgical Ischemic-Reperfusion Injury, Nashville, NC (United States), 21 Sep 1997
ISSN: 0003-4975 CODEN: ATHSAK
DOCUMENT TYPE: Journal; Conference
BIBLIOGRAPHIC LEVEL: Analytic
COUNTRY: United States
LANGUAGE: English
AVAILABILITY: INIST-13779, 354000080429550870

AN 2000-0017130 PASCAL
CP Copyright .COPYRGT. 2000 INIST-CNRS. All rights reserved.
AB Background. Monophosphoryl lipid-A (MLA) has a late window (24 hours) of cardioprotection against acute myocardial infarction. It is not known whether MLA, **administered**, 24 hours before surgery, attenuates intraoperative ventricular dysfunction "stunning" associated with aortic cross-clamping and reperfusion during elective cardiac surgery. We determined the dose-response relationship between MLA and ventricular function in a canine model of global myocardial stunning in the absence of necrosis. The role of expression of inducible **heat shock protein** 70 (HSP 70i) was also investigated.
Methods. Mongrel dogs (n = 32) were intravenously injected with either a vehicle solution or 3, 5, 10, 35 ug/kg MLA. Twenty four hours later, dogs were anesthetized and instrumented, in situ, to monitor the left ventricular performance (the slope of regression between stroke-work and end diastolic length). Tissue samples were obtained to determine HSP70i using immunoblot analysis. After a period of equilibration on cardiopulmonary bypass, the aortic cross-clamp was applied at

normothermia for 30 minutes followed by 60 minutes of reperfusion. ATP and catabolites were determined in transmural myocardial biopsies. Triphenyl-tetrazolium chloride (TTC) staining was used to determine myocardial necrosis. Results. MLA treatment did not alter myocardial contractility or ATP metabolism. Global ischemia resulted in about 50% depletion of ATP and remained depressed during reperfusion in all groups. MLA-treated hearts had improved functional recovery in a dose dependent-manner. Significant recovery was observed at the highest dose (35 ug/kg) compared to the control group. Immunoblot analysis demonstrated significant increase in HSP 70i in the MLA-treated hearts. Conclusions. MLA exhibits a delayed (24 hours) window of protection against myocardial stunning associated with aortic cross-clamping. HSP70i expression may play a role in MLA-mediated cardioprotection.

L69 ANSWER 55 OF 64 PASCAL COPYRIGHT 2004 INIST-CNRS. ALL RIGHTS RESERVED. on STN

ACCESSION NUMBER: 1999-0517799 PASCAL
COPYRIGHT NOTICE: Copyright .COPYRGT. 1999 INIST-CNRS. All rights reserved.
TITLE (IN ENGLISH): Helicobacter pylori and Behcet's disease
AUTHOR: AVCI O.; ELLIDOKUZ E.; SIMSEK I.; BUEYUEKGEBIZ B.; GUENES A. T.
CORPORATE SOURCE: Department of Dermatology, Medical Faculty, Dokuz Eyluel University, Inciralti, Turkey; Department of Internal Medicine, Medical Faculty, Dokuz Eyluel University, Inciralti, Turkey; Department of Pediatrics, Medical Faculty, Dokuz Eyluel University, Inciralti, Turkey
SOURCE: Dermatology : (Basel), (1999), 199(2), 140-143, 13 refs.
ISSN: 1018-8665
DOCUMENT TYPE: Journal
BIBLIOGRAPHIC LEVEL: Analytic
COUNTRY: Switzerland
LANGUAGE: English
AVAILABILITY: INIST-4530, 354000088149400090
AN 1999-0517799 PASCAL
CP Copyright .COPYRGT. 1999 INIST-CNRS. All rights reserved.
AB Background: Recent investigation of the etiology of Behet's disease (BD) has focused on **heat shock proteins** (HSP) which belong to the HSP 60 family. Both the gastric pathogen Helicobacter pylori (HP) and BD may cause ulcers in the gastrointestinal tract and, HP expresses HSP 60. Objective: Whether HP is linked to the pathogenesis of BD or not, and to investigate the influence of HP eradication on clinical parameters of BD. Methods: Patients with BD were divided into two groups. Group I comprised 49 patients and was investigated for HP seroprevalence and compared with age- and sex-matched controls. Group II comprised 20 patients with BD and HP infection diagnosed by serological and endoscopic examinations as well as the rapid urease test (RUT). A 1-week eradication therapy was **administered** for HP infection. Patients were examined for the course of BD at monthly intervals. Two months after the eradication therapy, patients underwent an endoscopic examination and RUT for eradication control. Seven patients were excluded because of eradication failure. Thirteen patients were evaluated for the influence of HP eradication on clinical manifestations of BD. The number and size of oral and genital ulcers before the eradication and at the end of the follow-up period were compared statistically. Results: HP seroprevalence between patients with BD and controls did not show significant difference. In 13 patients with BD, the number and size of oral and genital ulcers diminished significantly and various clinical manifestations regressed after the eradication of HP. Conclusion: HP may be involved in the pathogenesis of BD.

L69 ANSWER 56 OF 64 USPATFULL on STN

ACCESSION NUMBER: 1998:75715 USPATFULL
TITLE: Vaccine compositions and methods useful in inducing

immune protection against arthritogenic peptides involved in the pathogenesis of rheumatoid arthritis

INVENTOR(S): Carson, Dennis A., Del Mar, CA, United States
Albani, Salvatore, San Diego, CA, United States

PATENT ASSIGNEE(S): The Regents of the University of California, Oakland, CA, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 5773570		19980630
APPLICATION INFO.:	US 1996-618464		19960315 (8)

RELATED APPLN. INFO.: Continuation-in-part of Ser. No. US 1994-246988, filed on 20 May 1994, now abandoned

DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Minnifield, Nita
LEGAL REPRESENTATIVE: Fish & Richardson P.C.
NUMBER OF CLAIMS: 8
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 5 Drawing Figure(s); 5 Drawing Page(s)
LINE COUNT: 1045
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Vaccine compositions useful in inducing immune protection in a host against arthritogenic peptides involved in the pathogenesis of rheumatoid arthritis are disclosed. Each vaccine composition provides antigenic dnaJp1 peptide (by including the peptide or a polynucleotide which encodes the peptide).

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L69 ANSWER 57 OF 64 USPATFULL on STN

ACCESSION NUMBER: 1998:33894 USPATFULL

TITLE: Methods for the treatment of neuronal damage associated with ischemia, hypoxia or neurodegeneration

INVENTOR(S): Alps, Brian J., Linlithgow, Scotland
Brown, Christine Mary, Glasgow, Scotland
Collins, Franklin D., Agoura Hills, CA, United States
Emmett, Caroline J., Belmont, CA, United States
Spedding, Michael, Le Vesinet, France
Russell, Deborah, Boulder, CO, United States
Finklestein, Seth P., Needham, MA, United States
Moskowitz, Michael A., Belmont, MA, United States
Whiting, Roger Lewis, Los Altos, CA, United States

PATENT ASSIGNEE(S): The General Hospital Corporation, Boston, MA, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 5733871		19980331
	WO 9308828		19930513
APPLICATION INFO.:	US 1995-30429		19950316 (8)
	WO 1992-US9618		19921106
			19950316 PCT 371 date
			19950316 PCT 102(e) date

RELATED APPLN. INFO.: Continuation-in-part of Ser. No. US 1991-790734, filed on 8 Nov 1991, now abandoned

DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Tsang, Cecilia J.
ASSISTANT EXAMINER: Touzeau, P. L.
LEGAL REPRESENTATIVE: Fish & Richardson P.C.
NUMBER OF CLAIMS: 4
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 8 Drawing Figure(s); 5 Drawing Page(s)
LINE COUNT: 1209
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Intravenous administration and pharmaceutically acceptable compositions of neurotrophic factors for treating neuronal damage in the central nervous system of individuals in need of such treatment are disclosed. The neuronal damage associated with ischemia, hypoxia, or neurodegeneration may result from stroke or cardiac arrest. This invention provides for the intravenous administration of neurotrophic factors such as bFGF, aFGF, NGF, CNTF, BDNF, NT3, NT4, IGF-I and IGF-II.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L69 ANSWER 58 OF 64 BIOTECHNO COPYRIGHT 2004 Elsevier Science B.V. on STN
DUPLICATE
ACCESSION NUMBER: 1998:29131895 BIOTECHNO
TITLE: Clonidine-induced heat-shock protein expression in rat aorta
AUTHOR: Moen R.J.; LaVoi K.P.; Zhang M.; Blake M.J.
CORPORATE SOURCE: Dr. M.J. Blake, Dept. of Pharmacology and Toxicology, Univ. of North Dakota School of Med., 501 N. Columbia Road, Grand Forks, ND 58203, United States.
SOURCE: Journal of Cardiovascular Pharmacology and Therapeutics, (1998), 3/2 (171-184), 35 reference(s)
CODEN: JCPTFE ISSN: 1074-2484
DOCUMENT TYPE: Journal; Article
COUNTRY: United States
LANGUAGE: English
SUMMARY LANGUAGE: English
AN 1998:29131895 BIOTECHNO
AB Background: Restraint-stress and administration of drugs that precipitate hypertension induce **heat-shock protein** (HSP) expression in the aorta. The exact mechanism supporting this hypertension-related HSP response is unclear because HSP induction is blocked by receptor-selective and nonselective antihypertensive agents. Methods and Results: To identify mechanisms contributing to the pharmacological/physiological regulation of the HSP response in cardiovascular tissues, we **administered** clonidine to awake and freely moving animals to determine its effect on HSP expression in vivo. Inconsistent with previous work, we found that clonidine produced a dose-dependent and transient increase in HSP70 mRNA levels in the aorta. No other tissue examined displayed an HSP response after clonidine administration. Clonidine-induced HSP expression was not restricted to the HSP70 family; HSP89α, HSP89β, and HSP60 were also induced. Interestingly, no heat-shock element-binding activity was observed after clonidine administration, suggesting that unusual transcriptional regulatory mechanisms mediate this response. Yohimbine and nifedipine blocked HSP70 mRNA expression, whereas isoproterenol, mecamylamine, and reserpine had no effect. Conclusions: The functional consequence of HSP expression in cardiovascular tissues may be to alter the responsiveness of cells in these tissues to subsequent drug or stress exposures, thereby implicating the HSP response as an important component of cardiovascular homeostasis. If so, treatment of mammalian organisms with drugs capable of inducting selective HSP expression in **vascular** tissue may alter the progression of cardiovascular **disease** processes.

L69 ANSWER 59 OF 64 BIOTECHDS COPYRIGHT 2004 THOMSON DERWENT/ISI on STN
ACCESSION NUMBER: 1997-06524 BIOTECHDS
TITLE: Adeno-associated virus vector for transfecting heart and vascular tissue;
heterologous protein gene transfer to mammal cardiac muscle cell or **vascular** endothelial cell for cardiovascular **disease** gene therapy
AUTHOR: Kaplitt M J; Diethrich E B
PATENT ASSIGNEE: Univ.New-York-Rockefeller
LOCATION: New York, NY, USA.
PATENT INFO: WO 9712050 3 Apr 1997
APPLICATION INFO: WO 1996-US15446 26 Sep 1996
PRIORITY INFO: US 1995-534351 27 Sep 1995

DOCUMENT TYPE: Patent
LANGUAGE: English
OTHER SOURCE: WPI: 1997-212909 [19]
AN 1997-06524 BIOTECHDS
AB A novel adeno-associated virus vector (AAV) contains: AAV sequences containing replication and packaging signals of AAV; and a gene encoding a protein which when expressed in cardiac muscle cells or vascular endothelial cells, improves cardiac or vascular function. The gene encodes streptokinase, urokinase (EC-3.4.21.73), tissue plasminogen-activator, superoxide-dismutase (EC-1.15.1.1), **heat shock protein** (mol.weight 70,000), plate-derived growth factor, fibroblast growth factor, epidermal growth factor, transforming growth factor, insulin growth factor, low density lipoprotein receptor, a protein involved in angiogenesis, renin angiotensin, or an enzyme involved in the activation of renin (EC-3.4.99.19) or angiotensin. The target cell is selected from Primate, Rodenta, Carnivora and Arteriodactyla and is preferably human. The AAV vectors are **administered** to mammal heart cells via a catheter inserted into a peripheral artery. Such a method may be used for cardiovascular gene therapy. (45pp)

L69 ANSWER 60 OF 64 WPIDS COPYRIGHT 2004 THOMSON DERWENT on STN
ACCESSION NUMBER: 1996-499136 [50] WPIDS
DOC. NO. CPI: C1996-155965
TITLE: Pharmaceutical compsn. containing HSP47 production inhibitor e.g. malt extract, flavonoid or tocopherol derivative - used for inhibiting collagen biosynthesis e.g. in treatment of liver cirrhosis or rheumatoid arthritis.
DERWENT CLASS: B02 B04 B05 D16
INVENTOR(S): KIYOSUKE, Y; MORINO, M; SHIRAKAMI, T; YOSHIKUMI, C
PATENT ASSIGNEE(S): (KURE) KUREHA CHEM IND CO LTD
COUNTRY COUNT: 7
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
EP 742012	A2	19961113	(199650)*	EN	23
R: DE FR GB NL					
JP 08301757	A	19961119	(199705)		10
JP 08301781	A	19961119	(199705)		10
JP 08301784	A	19961119	(199705)		9
AU 9652140	A	19961219	(199708)		
CA 2175985	A	19961111	(199711)		
JP 09012459	A	19970114	(199712)		8
JP 09040553	A	19970210	(199716)		9
JP 09040556	A	19970210	(199716)		7
AU 689036	B	19980319	(199825)		
JP 2892300	B2	19990517	(199925)		9
JP 2933511	B2	19990816	(199938)		9
JP 3003978	B2	20000131	(200010)		9

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
EP 742012	A2	EP 1996-107224	19960508
JP 08301757	A	JP 1995-136028	19950510
JP 08301781	A	JP 1995-136027	19950510
JP 08301784	A	JP 1995-136029	19950510
AU 9652140	A	AU 1996-52140	19960507
CA 2175985	A	CA 1996-2175985	19960507
JP 09012459	A	JP 1995-186302	19950629
JP 09040553	A	JP 1995-211274	19950728
JP 09040556	A	JP 1995-210935	19950727
AU 689036	B	AU 1996-52140	19960507
JP 2892300	B2	JP 1995-136029	19950510

JP 2933511	B2	JP 1995-211274	19950728
JP 3003978	B2	JP 1995-186302	19950629

FILING DETAILS:

PATENT NO	KIND		PATENT NO
AU 689036	B	Previous Publ.	AU 9652140
JP 2892300	B2	Previous Publ.	JP 08301784
JP 2933511	B2	Previous Publ.	JP 09040553
JP 3003978	B2	Previous Publ.	JP 09012459

PRIORITY APPLN. INFO: JP 1995-211274 19950728; JP 1995-136027 19950510; JP 1995-136028 19950510; JP 1995-136029 19950510; JP 1995-186302 19950629; JP 1995-210935 19950727

AN 1996-499136 [50] WPIDS

AB EP 742012 A UPAB: 19961211

A pharmaceutical compsn. contains an inhibitor (I) of HSP47 production and a carrier. (I) is a malt extract, a flavonoid cpd., a protein-bound-polysaccharide obtd. from Coriolus versicolor, a paeoniflorin (PE) derivative, a tocopherol derivative or a ferulic acid derivative

The malt extract is obtd. by saccharifying a malt, filtering, extracting the filter cake with water and/or a hydrophilic solvent (pref. under alkaline conditions) and removing low mol. weight fractions from the obtd. liquid extract. An extract obtd. under alkaline conditions is pref. neutralised, the obtd. ppte. is removed and the fraction of mol. weight 10000 is removed from the supernatant; or alternatively the extract is acidified to pH 3-5, the precipitated protein is removed, the supernatant is neutralised, the obtd. ppte. is removed and the fraction of mol. weight 10000 is removed from the supernatant. The flavonoid cpd. is e.g. quercetin, rutin, baicalein or catechin. The glycoprotein is from the mycelium, broth or fruiting body of C. versicolor, and is especially PSK. The PF derivative is PF, the tocopherol derivative is alpha-tocopherol and the ferulic acid. (I) includes tea extracts containing tea catechin, plant extracts containing PF, peony root extracts, plant extracts containing ferulic acid and rice extracts.

USE - By inhibiting production of HSP47, a **heat shock protein** of mol. weight 47 kDa which stimulates accumulation of collagen molecules in the extracellular matrix, (I) inhibits collagen biosynthesis and is useful for treating **diseases** associated with excessive production of extracellular matrix. Typically, (I) is used for treating liver cirrhosis, interstitial lung **disease**, chronic renal failure (or causative **diseases** such as IgA nephropathy, focal glomerulosclerosis, membrano-proliferative nephritis, diabetic nephropathy, chronic interstitial nephritis or chronic glomerulonephritis), post-operative or burn scars, keloid or hypertrophic scars after accidents, scleroderma, arteriosclerosis or rheumatoid arthritis. Since collagen synthesis is important in **vascular** growth, (I) is also useful for treating or preventing **diseases** involving abnormal **vascular** growth, e.g. diabetic retinopathy, retrolental fibroplasia, vascularisation due to corneal transplantation, glaucoma, eye tumours, trachoma, psoriasis, pyogenic granuloma, haemangioma, angiofibroma, hypertrophic scar, granulation, atherosclerosis or other tumours. (I) also inhibits cancer metastasis. Daily dose is 1-1000 mg, orally or parenterally. (I) may also be **administered** topically.

Dwg.0/4

L69 ANSWER 61 OF 64 PASCAL COPYRIGHT 2004 INIST-CNRS. ALL RIGHTS RESERVED. on STN

ACCESSION NUMBER: 1997-0051694 PASCAL

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TITLE (IN ENGLISH): Repeated hyperbaric oxygen induces ischemic tolerance in gerbil hippocampus

AUTHOR: WADA K.; ITO M.; MIYAZAWA T.; KATOH H.; NAWASHIRO H.; SHIMA K.; CHIGASAKI H.
CORPORATE SOURCE: Saitama 359, Japan; Kanagawa, Japan
SOURCE: Brain research, (1996), 740(1-2), 15-20
ISSN: 0006-8993 CODEN: BRREAP
DOCUMENT TYPE: Journal
BIBLIOGRAPHIC LEVEL: Analytic
COUNTRY: Netherlands
LANGUAGE: English
SUMMARY LANGUAGE: English
AVAILABILITY: INIST-12895, 354000061290440006
AN 1997-0051694 PASCAL
CP Copyright .COPYRGT. 1997 Elsevier Science B.V. All rights reserved.
AB Copyright (c) 1996 Elsevier Science B.V. All rights reserved. Hyperbaric oxygen (HBO; 100 oxygen at 2 atmospheres absolute) was **administered** for 1 h to male Mongolian gerbils either for a single session or every other day for five sessions. Two days after HBO pretreatment, the gerbils were subjected to 5 min of forebrain ischemia by occlusion of both common carotid arteries under anesthesia. Seven days after recirculation, neuronal density per 1-mm length of the CA1 sector in the hippocampus was significantly better preserved in the five-session HBO pretreatment group (n=10: 175.7 (47.8/mm, 54.9 of normal) than in the ischemic control group (n=10: 26.2 (11.6/mm, 8.0 of normal) and in the single-session HBO pretreatment group (n=7: 37.3 (21.7/mm, 11.4 of normal). Immunohistochemical staining for the 72-kDa **heat-shock protein** (HSP-72) in the CA1 sector performed 2 days following pretreatment revealed that the five-session HBO pretreatment increased the amount of HSP-72 present compared with that in the ischemic control group and in the single HBO pretreatment group. These results suggest that tolerance against ischemic neuronal damage was induced by repeated HBO pretreatment, which is thought to occur through the induction of HSP-72 synthesis.

L69 ANSWER 62 OF 64 DGENE COPYRIGHT 2004 THOMSON DERWENT on STN
ACCESSION NUMBER: AAE11757 Protein DGENE
TITLE: Treating a **vascular disorder**, involves **administering** a composition comprising **heat shock protein**, its fragment or analog, by mucosal surface, pulmonary tract, oral or enteral route, or by inhalation -
INVENTOR: Weiner H L; Maron R; Libby P
PATENT ASSIGNEE: (BGHM)BRIGHAM & WOMENS HOSPITAL INC.
PATENT INFO: WO 2001068124 A2 20010920 49p
APPLICATION INFO: WO 2001-US8351 20010315
PRIORITY INFO: US 2000-189855P 20000315
DOCUMENT TYPE: Patent
LANGUAGE: English
OTHER SOURCE: 2001-611383 [70]
DESCRIPTION: Chlamydophila pneumoniae heat shock protein 60 (HSP60).
AN AAE11757 Protein DGENE
AB The patent discloses methods for treating **vascular disorders** in mammals. The method involves **administering** a composition comprising at least one agent selected from **heat shock protein** (HSP), its fragment or analogue, through mucosal surface, pulmonary tract, oral or enteral route or by inhalation. Compositions comprising HSP are useful for treating and suppressing a **vascular disorder**, including cell-mediated immune response, an antibody-mediated immune response, cell-mediated inflammatory **disorder**, atherosclerosis, allergic angiitis, Behcet's syndrome, granulomatosis (Churg-Strauss **disease**), Cogan's syndrome, graft-versus-host **disease** (GvHD), Henoch-Schonlein purpura, Kawasaki **disease**, leucocytoclastic vasculitis, polyarteritis nodosa (PAN), microscopic polyangiitis, polyangiitis overlap syndrome, Takayasu's arteritis, temporal arteritis, transplant rejection, Wegener's granulomatosis and thromboangiitis obliterans (Buerger's **disease**). They are useful for reducing

the level of proinflammatory Th1 cytokines and also for increasing the level of antiinflammatory Th2 cytokines. The present sequence is **heat shock protein** 60 (HSP60) from Chlamydophila pneumoniae.

L69 ANSWER 63 OF 64 DGENE COPYRIGHT 2004 THOMSON DERWENT on STN
ACCESSION NUMBER: AAE11756 Protein DGENE
TITLE: Treating a **vascular disorder**, involves **administering** a composition comprising **heat shock protein**, its fragment or analog, by mucosal surface, pulmonary tract, oral or enteral route, or by inhalation -
INVENTOR: Weiner H L; Maron R; Libby P
PATENT ASSIGNEE: (BGHM)BRIGHAM & WOMENS HOSPITAL INC.
PATENT INFO: WO 2001068124 A2 20010920 49p
APPLICATION INFO: WO 2001-US8351 20010315
PRIORITY INFO: US 2000-189855P 20000315
DOCUMENT TYPE: Patent
LANGUAGE: English
OTHER SOURCE: 2001-611383 [70]
DESCRIPTION: Human heat shock protein 60 (HSP60).
AN AAE11756 Protein DGENE
AB The patent discloses methods for treating **vascular disorders** in mammals. The method involves **administering** a composition comprising at least one agent selected from **heat shock protein** (HSP), its fragment or analogue, through mucosal surface, pulmonary tract, oral or enteral route or by inhalation. Compositions comprising HSP are useful for treating and suppressing a **vascular disorder**, including cell-mediated immune response, an antibody-mediated immune response, cell-mediated inflammatory **disorder**, atherosclerosis, allergic angiitis, Behcet's syndrome, granulomatosis (Churg-Strauss **disease**), Cogan's syndrome, graft-versus-host **disease** (GvHD), Henoch-Schonlein purpura, Kawasaki **disease**, leucocytoclastic vasculitis, polyarteritis nodosa (PAN), microscopic polyangiitis, polyangiitis overlap syndrome, Takayasu's arteritis, temporal arteritis, transplant rejection, Wegener's granulomatosis and thromboangiitis obliterans (Buerger's **disease**). They are useful for reducing the level of proinflammatory Th1 cytokines and also for increasing the level of antiinflammatory Th2 cytokines. The present sequence is **heat shock protein** 60 (HSP60) from human.

L69 ANSWER 64 OF 64 DGENE COPYRIGHT 2004 THOMSON DERWENT on STN
ACCESSION NUMBER: AAE11755 Protein DGENE
TITLE: Treating a **vascular disorder**, involves **administering** a composition comprising **heat shock protein**, its fragment or analog, by mucosal surface, pulmonary tract, oral or enteral route, or by inhalation -
INVENTOR: Weiner H L; Maron R; Libby P
PATENT ASSIGNEE: (BGHM)BRIGHAM & WOMENS HOSPITAL INC.
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DESCRIPTION: Mycobacterium tuberculosis heat shock protein 65 (HSP65).
AN AAE11755 Protein DGENE
AB The patent discloses methods for treating **vascular disorders** in mammals. The method involves **administering** a composition comprising at least one agent selected from **heat shock protein** (HSP), its fragment or analogue, through mucosal surface, pulmonary tract, oral or enteral route or by inhalation. Compositions comprising HSP are useful for treating and suppressing a **vascular disorder**, including cell-mediated immune

response, an antibody-mediated immune response, cell-mediated inflammatory **disorder**, atherosclerosis, allergic angiitis, Behcet's syndrome, granulomatosis (Churg-Strauss **disease**), Cogan's syndrome, graft-versus-host **disease** (GvHD), Henoch-Schonlein purpura, Kawasaki **disease**, leucocytoclastic vasculitis, polyarteritis nodosa (PAN), microscopic polyangiitis, polyangiitis overlap syndrome, Takayasu's arteritis, temporal arteritis, transplant rejection, Wegener's granulomatosis and thromboangiitis obliterans (Buerger's **disease**). They are useful for reducing the level of proinflammatory Th1 cytokines and also for increasing the level of antiinflammatory Th2 cytokines. The present sequence is **heat shock protein** 65 (**HSP65**) from Mycobacterium tuberculosis.

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